

1. On the Reactions of Diazoalkyls with 1-Phenyl-2-Methylurazole.
2. On the Rearrangement of the Tautomeric Salts of 1,4-Diphenyl-5-Thionurazole and 1,4-Diphenyl-5-Thiolurazole.

DISSERTATION

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES OF
THE JOHNS HOPKINS UNIVERSITY IN CONFORMITY
WITH THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF
PHILOSOPHY.

BY SIDNEY NIRDLINGER

1909.

Diss. Baltimore.

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I. On the Reactions of Diazoalkyls with 1-Phenyl-2-Methylurazole.

THEORETICAL.

The efforts to find the exact position of the two acid hydrogen atoms of phenylurazole¹ have shown that this compound is to be classed, from a theoretical point of view, among the most interesting and important of all tautomeric substances. The presence of two movable hydrogen atoms and the consequent possibilities of obtaining a large number of isomeric derivatives, each of which can be estimated quantitatively under easily regulated conditions, has made possible a quantitative study of the tautomeric phenomena presented, and the results have an important bearing on the question of tautomerism in general.

From a quantitative study of the reactions of the salts of phenylurazole, phenyl-4-methylurazole, and phenyl-3-thio-

¹ Am. Chem. J., **27**, 118; **31**, 185; **32**, 606; **37**, 71, 361; **38**, 1; **39**, 125. Ber. d. chem. Ges., **35**, 553; **36**, 3139; **37**, 184, 618.

urazole, in all of which it has been shown by Acree and Brunel¹ that there are probably two or more tautomeric forms whose equilibrium constants are established practically instantaneously under the conditions maintained in the work, Acree² and his collaborators have been able to show that the results are not in harmony with the theories of Comstock,³ Wheeler,⁴ Nef,⁵ and Michael,⁶ but are in accordance with the theory proposed by Acree,⁷ namely, that *in all cases in which these tautomeric urazoles give two or more stable isomeric products as the result of a reaction, they do so because they exist in two or more forms in equilibrium, each of which reacts independently, or because one form is changed into stable derivatives through two or more side reactions.* The ratio of the products obtained depends entirely on the equilibrium conditions and the several reaction velocities. The mathematical treatment of this theory has been worked out in detail for the most part⁸ and all the experimental results are in harmony with what the theory demands. This theory is not being followed blindly, however; it is used as a working hypothesis and is being subjected to the same rigid scrutiny that was applied to the others. It will be discarded as soon as it has outlived the "day of usefulness" that is the glory of man or theory.

Since, however, all the work up to the present has been done on the metallic salts, it seemed desirable to study the reactions of the urazole acids themselves, the compounds chosen being those that under the conditions studied established the equilibrium practically instantaneously.

This report is confined to the reactions of the diazoalkyls with the urazole acids. The diazoalkyls were chosen as the alkylating agents because (1) they all, with the very important exception of diazopropylene, $\text{CH}_2 = \text{CH}-\text{CH} = \text{N}_2$, react *very rapidly* with the urazole acids, and because (2) they yield

¹ Brunel: Diss., Johns Hopkins Univ., 1906.

² Am. Chem. J., **38**, 1; **39**, 125, 226. Ber. d. chem. Ges., **41**, 3199.

³ Ber. d. chem. Ges., **23**, 2274. Am. Chem. J., **12**, 493; **13**, 514, 525.

⁴ Am. Chem. J., **21**, 187; **23**, 135; **30**, 28.

⁵ Ann. Chem. (Liebig). **266**, 52; **276**, 200; **277**, 59, 83, etc.

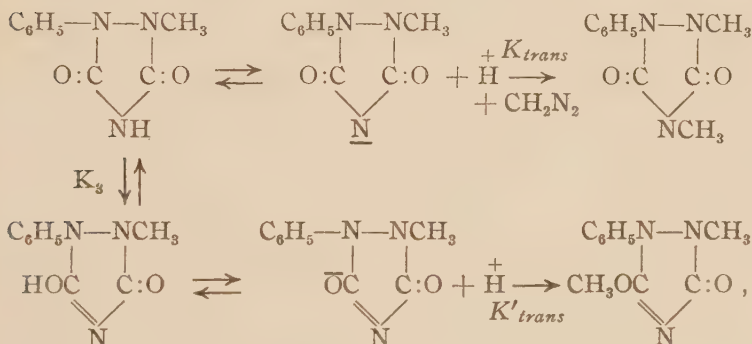
⁶ J. prakt. Chem., [2] **37**, 469; **45**, 580; **46**, 189, etc.

⁷ Loc. cit.

⁸ Am. Chem. J., **38**, 1.

a mixture of isomeric esters which can be worked with quantitatively. *It was believed that this would give a new method for studying the question whether the salts of urazoles have equilibrium constants different from those of the acids, and Mr. E. K. Marshall has now shown that such differences really exist.* As was predicted, these differences are too small to be measured easily by conductivity methods. The diazoalkyl reacts with the urazole acid liberated from the salt by the action of acids, water, alcohol, etc., before it changes into the equilibrium condition, a change that is too small and too rapid to be followed by conductivity measurements.

The salts, when treated with an alkylating agent, have all given a constant ratio of esters in any given series of experiments, but it does not follow that this would be true for the acids.¹ If we consider the following scheme,



¹ Acree showed that 1-phenyl-2-methylurazole and 1-phenyl-4-methylurazole yield with diazomethane *stable* isomeric *N*-esters and *O*-esters. This proves that these urazoles must exist either (A) in only one tautomeric form which reacts with the diazomethane in two (or more) independent side reactions, or (B) in two or more tautomeric forms; in this case (1) each form may react independently with the diazomethane and yield its corresponding ester, or two (or more) esters by side reactions, or (2) one form alone may yield the two esters by side reactions. The probability of (A) can be eliminated by the following evidence: The salts of 1-phenyl-2-methylurazole and 1-phenyl-4-methylurazole exist in two tautomeric forms and the two acids are liberated when a strong mineral acid is added. But it might be thought that one of these tautomeric acids immediately changes into the other and that the acid actually isolated and worked with exists in only one form. But the urazole acids are themselves also weak bases; either tautomeric form of the acid would therefore form a salt with other molecules of itself, which salt would partially rearrange into the other tautomeric salt. Both tautomeric salts are constantly being hydrolyzed, alcoholized, etc., into the corresponding two tautomeric acids, which are therefore generally in solution together. Traces of alkalies from glass, etc., could also bring

we readily see that the constancy of ratio between the isomeric esters is only a special case, due either to the fact (1) that the constants for the velocity of establishment of K_3 , which is the equilibrium ratio between the molecular enol and keto forms, are very large in comparison with K_{trans} , the velocity constant for the reaction of the keto form with the diazo compound, and K'_{trans} , the corresponding constant for the enol form; or to the fact (2) that, if the constants for the velocity of establishment of K_3 are very small, K'_3 , the ratio of the molecular enol and keto forms at the particular time t in question, is approximately equal to $\frac{c_2}{c_3}$. In K_{trans} and K'_{trans} no consideration is taken of the fact that the acid is ionized or that the reaction may either be ionic or molecular, or both. If α is the percentage of ionization of the keto form of the acid and the reaction is ionic we would have $K_{trans} = \alpha K_{1trans}$, in which K_{1trans} is the real reaction constant.¹ In any case K_{trans} and K'_{trans} are equal to the real reaction constants multiplied by their corresponding factors, the ratio of which factors probably does not change appreciably during the reaction periods measured.

In every other case we would expect the ratio of esters to be dependent on the time. For we have $\frac{c}{c'} = K'_3$ at the time t , and

$$\frac{dc_2}{dt} = \frac{K_{trans}K'_3}{1 + K'_3} (c + c_1 - c_2 - c_3)^2, \text{ and}$$

$$\frac{dc_3}{dt} = \frac{K'_{trans}}{1 + K'_3} (c + c_1 - c_2 - c_3)^2,$$

in which c is the concentration of the practically undissociated keto acid present, c_1 the concentration of the enol acid, c_2 the concentration of the keto ester formed, and c_3 that of the

about such tautomeric changes. I believe that each form of the acid yields (1) the corresponding ester, and not (2) two isomeric esters through side reactions; but this latter possibility is being tested experimentally and practically all of the conclusions arrived at in the following pages can be deduced as readily from one point of view as from the other. I therefore use the former (1) in the following pages for the sake of clearness and convenience, believing it to be nearest the truth.

¹ Ber. d. chem. Ges., **41**, 3212.

enol ester. When equimolecular amounts of acid and diazoalkyl are used, the concentration of the latter is also expressed by $(c + c_1 - c_2 - c_3)$. Dividing and integrating, we obtain, if c_2 and c_3 are zero when $t = 0$,

$$\frac{c_2}{c_3} = \frac{K'_3 K_{trans}}{K'_{trans}}.$$

But if K'_3 is a function of the time, t , then the ratio $\frac{c_2}{c_3}$ would vary accordingly. The reactions between the urazole salts mentioned above and the alkyl halides show most conclusively that the time function of K'_3 need not be considered in the case of these salts. The salts, however, are very different from the acids, being highly ionized and comparable in every way with the salts of strong acids, while the acids themselves are very little ionized,¹ and far less reactive towards alkyl halides. Thus, since the urazole acids react so exceedingly rapidly with diazoalkyls,² we might expect different results from some of the urazole acids³ and then we might get some clue as to the rapidity of establishment of K_3 or its value.

If K'_3 changed very slowly in comparison with the rate of alkylation, then the addition of a small fraction of a molecular equivalent of diazomethane would give a ratio of esters approximately equal to $\frac{cK_{trans}}{c_1 K'_{trans}}$, while the addition of a molecular equivalent would give a ratio approximating K'_3 . The addition of different amounts of diazomethane would give a variable ratio, then, unless $K_{trans} = K'_{trans}$, or, in other words, $\frac{c_2}{c_3} = K'_3$.⁴ This last possibility can be eliminated by using other diazoalkyls such as diazoethane, -propane, -butane, etc., which give different values of $\frac{c_2}{c_3}$, which would then not be equal to K'_3 . On the other hand, if K'_3 is not a function of

¹ Am. Chem. J., **39**, 126.

² Ber. d. chem. Ges., **27**, 1889.

³ I have found this to be the case with the tautomeric 1-phenyl-3-oxy-4-phenyl-5-thiolurazole and 1-phenyl-3-hydroxy-4-phenyl-5-thionurazole which change into each other slowly. See part Second.

⁴ Am. Chem. J., **38**, 7.

t , when compared with K_{trans} and K'_{trans} , we should expect a constant ratio of esters as in the case of the salts. The experimental evidence shows conclusively that we do get a constant ratio of esters for variable amounts of diazoalkyl used. We must conclude, therefore, that however rapidly the diazoalkyls act with 1-phenyl-2-methylurazole, the various equilibrium constants are established very much more rapidly. Mr. E. K. Marshall is studying these reactions at low temperatures to see if the changes take place slowly enough to be measured under those conditions.

Owing to the fact that the diazoalkyls are decomposed so rapidly by water,¹ it was impossible to use aqueous solutions in studying these reactions. It was hoped that aqueous solutions could be used because Acree and Shadinger² have determined the affinity constants of a number of these urazoles in water. An attempt was made to suspend the 1-phenyl-2-methylurazole in water and add a ligroin solution of diazomethane, but only a few milligrams of ester were obtained. The amount was too small to analyze and besides it may have been formed from the small amount of the acid which was dissolved by the ligroin. With an ether solution of diazomethane and an aqueous solution of the urazole acid no better results were obtained. This difficulty with the aqueous solutions, combined with the extreme rapidity of the reaction, made an exact study of its mechanism impossible, but still we have some clues as to its general nature. *Whatever the nature of the reaction between the diazoalkyl and one of the tautomeric forms of the acid, the reaction between it and the other form must be of the same APPARENT³ order.* Otherwise we would not get a constant ratio of esters for variable amounts

¹ von Pechmann: Ber. d. chem. Ges., **27**, 1889.

² Am. Chem. J., **39**, 124.

³ The possibility that one ester is formed by a bimolecular reaction, for example, and the other ester from the same or another tautomeric form of the acid by a far more complicated but apparently bimolecular reaction, as Julius Meyer (Z. physik. Chem., **66**, 81; **67**, 257) has found in other very interesting cases, seems to be excluded by the fact that *all* diazoalkyls yield ratios of esters which do not vary with different concentrations and different time periods. It would be in only one case in a very large number that *even two* diazoalkyls could behave in such a way, as a large number of constants would be involved in the two sets of reactions yielding the two esters. The two sets of reactions are therefore probably very similar.

of alkylating agent used. For while the theory of side reactions of the same order requires that the ratio of products during any one reaction be constant, no matter what the order of the reactions,¹ since it depends solely on the ratio of the velocity constants, at the same time, even if K'_3 is constant, a changing ratio of products will be obtained when the two reactions are of a different order, since the rates of formation of the two esters will not be changed in the same way. If, for example, the keto ester is formed by a bimolecular reaction and the enol ester by the following trimolecular reaction between the urazole acid and the diazoalkyl, the concentration of which at any moment is designated by $(A - c_2 - c_3)$, we have

$$\frac{dc_2}{dt} = \frac{K_{trans}K_3}{1 + K'_3} (c + c_1 - c_2 - c_3)(A - c_2 - c_3),$$

$$\frac{dc_3}{dt} = \frac{K'_{trans}}{1 + K'_3} (c + c_1 - c_2 - c_3)(A - c_2 - c_3)^2, \text{ and}$$

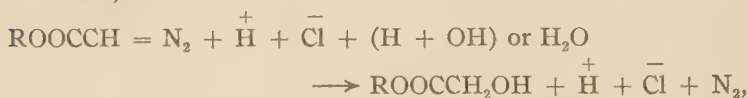
$$\frac{dc_2}{dc_3} = \frac{K_{trans}K'_3}{K'_{trans}} \cdot \frac{1}{(A - c_2 - c_3)}.$$

On integrating the last equation we would get an expression involving $(A - c_2 - c_3)$. Since K'_3 is a constant the ratio $\frac{c_2}{c_3}$ would then depend on $(A - c_2 - c_3)$ or the concentration of the diazoalkyl, which is a function of t , and $\frac{c_2}{c_3}$ would therefore vary with t . Since we get a constant ratio of esters from those diazoalkyls which react very rapidly, as well as from diazopropylene, which reacts very slowly, we know that the two reactions are of the same apparent order.

There is no experimental evidence from this work as to whether the diazoalkyls form intermediate complex anions or cations. It seems probable that diazomethane is basic in character and would form the complex cation $\text{CH}_2\text{N}_2\text{H}^+$. These complex ions might react with the urazole ions or the urazole molecules; very little is really known about this reaction. It follows from equations (1) and (2), on pages 14-15,

¹ Acree: Am. Chem. J., **38**, 1-8. Wegscheider: Z. physik. Chem., **30**, 593.

that $\frac{C_{ei}}{C_{ki}} = K \frac{C_{e\ mol.}}{C_{k\ mol.}}$. In acid solutions, therefore, there is *always* practically a constant ratio of the ions and also of the molecules of the two tautomeric forms, and the fact that a constant ratio of esters is obtained, even when, as shown by Mr. Marshall, hydrochloric acid is added, does not give any evidence as to whether the ions or the undissociated molecules yield the esters. In the case of diazoacetic ester, which reacts thus,



the velocity is dependent upon the concentration of the hydrogen ions and is, according to Bredig and Fraenkel, therefore due to intermediate complex salt and ion formation.¹ These reactions may or may not be similar.

This problem also permits of the study of the question of abnormal hydrolysis of salts of tautomeric compounds.² The hydrolysis of the salts of strong bases and weak acids is expressed by the equation $K_{hyd} = \frac{K_w}{K_{affur}}$, in which K_{hyd} is the hydrolysis constant, K_w the ion product of water, and K_{affur} the affinity constant of the urazole acid. But if there are two tautomeric salts in equilibrium, the affinity constant of the acid is not a simple number and is dependent on the affinity constant of the keto form and on that of the enol form, or other reacting form, whatever its nature, both of which are formed by the hydrolysis of the corresponding salts. Taking the scheme on page 9, we see that the affinity constant of the keto form is

$$K_{affk} = \frac{(C_{ki} \times H)(1 + K_3)}{K_3 \times C_{ur}} \quad (1),$$

that of the enol form

¹ Ber. d. chem. Ges., **40**, 4015. Bredig: Chemische Kinetik des Diazoessigesters und ihre Anwendungen: Z. physik. Chem., **60**, 202.

² Ber. d. chem. Ges., **35**, 210; **39**, 2098; **37**, 2298, 2468; **39**, 1607, 2265. Z. physik. Chem., **47**, 618. For a fuller discussion see Acree: Am. Chem. J., **38**, 30-41.

$$K_{affe} = \frac{(C_{ei} \times H)(1 + K_3)}{C_{ur}} \quad (2),$$

and that of the total acid

$$K_{affur} = \frac{(C_{ki} + C_{ei}) \times H}{C_{ur}} = \frac{K_{affe} + K_3 K_{affk}}{1 + K_3} \quad (3),$$

in which K_{affk} is the affinity constant of the keto form, K_{affe} that of the enol form, K_{affur} that of the total acid, C_{ki} the concentration of the keto ions, C_{ei} that of the enol ions, and H that of the hydrogen ions. C_{ur} is the concentration of the molecular urazole acid, and K_3 has the usual significance. But if the affinity constants of the two forms are different, anything that will disturb K_3 will change the value of K_{affur} . We would then get a new value, K'_{hyd} , for the hydrolysis constant, which would be equal to $\frac{K_w}{K'_{affur}}$, in which K'_{affur} is the new affinity constant of the urazole acid. This could be brought about in certain cases by adding a salt which would not only have a different equilibrium constant, K'_3 ,¹ but would also introduce a new ratio $C'_{ki} : C'_{ei}$ into the solution. Now I have proved, by the application of the mass law to such a case, that all salts must have a constant ratio of the concentrations of the two anions; namely, that for the acid itself, $C_{ki} : C_{ei}$. Notwithstanding this, my experimental results seem to indicate that the addition of such a salt changes $C_{ki} : C_{ei}$ and hence K_3 . If this is true it may take place because the ordinary formula for the mass law does not hold in the rather concentrated solutions that I use, or because by the addition of the salt I am changing the *medium*, in which the values of K_1 , K_2 and K_3 , etc., may change. If this is true, then the addition of a diazoalkyl to a solution of 1-phenyl-2-methylurazole containing several molecular amounts of the sodium salt should give an abnormal ratio of esters, since not only the value of K_3 but also the ratio of the ionic forms changes. I actually obtain an increase of 5 per cent. in the amount of enol ester in the presence of the salt. This proves that there is either an increase in the ratio of the concentration of the

¹ Mr. Marshall and Mr. Doetsch have now shown this to be the case with the tautomeric forms of 1-phenyl-2-methylurazole and 1-phenyl-3-hydroxy-4-phenyl-5-thionurazole.

enol ions to that of the keto ions, or that there is a corresponding change in the ratio of the concentration of the *enol molecular* form to that of the keto molecular form, and these conclusions are beautifully substantiated by Mr. E. K. Marshall's proof that the acid liberated from the sodium salt and alkylated *at once* with diazomethane yields a higher ratio of enol ester to keto ester than does the same acid after it attains its equilibrium. This proves then that there must be a change in the affinity constant of this urazole acid in the presence of its salts—and hence a change in the hydrolysis constant. In the other cases, it now appears that some urazole acids will give a *lower* ratio of enol ester to keto ester, and others will hardly have the normal ratio changed, in the presence of the salt. In other words, it seems now that some urazole acids will give a hydrolysis constant which is abnormally high, others a normal hydrolysis constant, and still others an abnormally low hydrolysis constant.

All of the above reactions would necessarily be modified to some extent if the urazole salt causes a catalytic change in the two reaction velocities, or if any other reactions not considered above are found to be taking place. I realize that these reactions may be very complicated and that conclusions can be drawn only tentatively at present. But that the *sodium ions* do not produce this change is shown by the fact that sodium iodide did not cause an appreciable change in the ratio of esters, a difference of only 0.3 per cent. being observed. This is far less than the experimental error. It must yet be determined whether urazole ions can effect such catalytic changes. The following table shows the results obtained:

20 cc. 0.0523 Vol. Normal 1-Phenyl-2-methylurazole in Methyl Alcohol and 30 cc. Ethereal Diazoethane Solution.

	Conc. diazo sol. 0.0087	0.0174	0.0261	0.0348	
	Per cent. <i>N</i> -ester in total product.				Average.
I - Phenyl - 2 - methyl- urazole	69.0	67.1	68.4	67.5	68.0
I - Phenyl - 2 - methyl- urazole and 3 mols. sodium salt	64.0	64.5	62.3	61.1	63.0
I - Phenyl - 2 - methyl- urazole and 3 mols. NaI	68.7	67.2	66.6	68.3	67.7

EXPERIMENTAL.

Phenylurazole.—Phenylurazole was prepared according to the method described by Acree.¹ It melted at 261° – 264° without decomposition.

1-Phenyl-2-methylurazole. — The 1-phenyl-2-methylurazole used in this work was made as follows: Twenty grams of phenylurazole were suspended in 200 cc. of alcohol and the theoretical amount of aqueous potassium hydroxide was added. Then about two molecular amounts of methyl iodide were added and the whole mixture was boiled four hours under a return condenser. The solution was evaporated to remove the alcohol and the excess of methyl iodide, and then acidified and filtered. The precipitate was extracted with chloroform to separate the unchanged phenylurazole, which is insoluble. The chloroform solution was filtered and extracted with alkali, which removes the 1-phenyl-2-methyl- and 1-phenyl-3-methoxyurazole and leaves any dialkyl derivative in the chloroform. The alkaline extract was acidified and filtered and the precipitate was evaporated with concentrated hydrochloric acid several times to dryness on a water bath to hydrolyze the methoxy ester. Then the phenyl-2-methylurazole was extracted from the insoluble phenylurazole with chloroform, and the solid obtained by evaporating the chloroform was crystallized from alcohol. From 20 grams of phenylurazole 8.5 grams of 1-phenyl-2-methylurazole melting at 185° – 186° , 0.5 gram melting at 175° – 178° and a residue of 1.5 grams of esterified product were obtained. The unchanged phenylurazole was recovered.

ON SOME 1-PHENYL-2-METHYL-4-ALKYLURAZOLES.

(BY WM. J. HEAPS.)

As the reactions of 1-phenyl-2-methylurazole are being studied extensively in this laboratory, it was thought desirable to make various 4-alkyl derivatives of it in order to characterize them. The 1-phenyl-2-methylurazole used in this work was made in the usual way and melted sharply at 185° .

¹ Am. Chem. J., **38**, 56.

1-Phenyl-2-methyl-4-ethylurazole.—To 5 grams of dry 1-phenyl-2-methylurazole were added 22.5 cc. of a normal solution of potassium hydroxide and then 60 cc. alcohol and 1.2 molecules of methyl iodide. The mixture was boiled on the water bath under a return condenser for 6 hours, the alcohol evaporated off and the residue evaporated to dryness with hydrochloric acid in order to saponify any *O*-ester present. An excess of alkali was added and the *N*-ester extracted with chloroform and recrystallized from alcohol. It was a white solid, soluble in alcohol, ether and chloroform, and melting at 112°. Yield, 2.5 grams.

Hydrolysis.—The ester was hydrolyzed in small tubes with alcoholic hydrochloric acid in the usual way¹ to see if any *O*-ester were present, but only a trace was found mixed with the *N*-ester.

0.1195 gram of ester lost 0.0009 gram, or 0.75 per cent.

Phenyl-2-methyl-4-propylurazole.—This was made from sodium phenyl-2-methylurazole and propyl iodide in the usual way: 2.4 grams of ester melting at 75° were obtained from 5 grams of phenyl-2-methylurazole. The hydrolysis showed the substance to be 99 per cent. pure. Hydrolysis:

0.101 gram of ester lost 0.001 gram, or 1 per cent.

0.1111 gram of ester lost 0.0008 gram, or 0.7 per cent.

Analysis:

0.1764 gram substance gave 0.3997 gram CO₂.

	Calculated for C ₁₂ H ₁₅ O ₂ N ₃ .	Found.
N	61.7	61.8

Phenyl-2-methyl-4-butylurazole.—This was made from sodium phenyl-2-methylurazole and butyl iodide. The ester is a heavy oil and could not be made to solidify, although many different solvents were used. That it was practically freed from the isomeric *O*-ester by the treatment with the alcoholic hydrochloric acid is shown by the following analysis:

Hydrolysis:

0.1143 gram of oil lost 0.0006 gram, or 0.5 per cent.

¹ See page 23.

Phenyl-2-methyl-4-isoamylurazole.—This ester was prepared in the usual way from sodium phenyl-2-methylurazole and isoamyl iodide. Two grams of phenyl-2-methylurazole gave 0.95 gram ester melting at 179° . The ester was soluble in alcohol, ether and chloroform. The treatment with alcoholic hydrochloric acid removed nearly all of the isomeric *O*-ester.

Hydrolysis;

0.1189 gram ester lost 0.0026 gram, or 2 per cent.

ON THE VELOCITY OF ALKYLATION OF THE SODIUM AND SILVER SALTS OF PHENYL-2-METHYLURAZOLE.

It was thought desirable to measure the values of the alkylation constants, and the ratios of esters formed, in the reactions between the salts of 1-phenyl-2-methylurazole and methyl and ethyl iodide, in order to get an indication of its properties and to compare it with 1-phenyl-4-methylurazole.¹ The sodium 1-phenyl-2-methylurazole was made by the method described by Shadinger.² The acid suspended in water was carefully neutralized by adding the theoretical amount of acid sodium carbonate and the resulting solution was evaporated on the water bath to dryness, water added and the evaporation to dryness repeated several times. Then the salt was crystallized once from water and dried in an air bath at 115° . It was neutral to phenolphthalein and perfectly white. In making the silver salt the 1-phenyl-2-methylurazole³ was dissolved in the theoretical amount of potassium hydroxide and one molecular equivalent of silver nitrate was added. The white precipitate formed was filtered off, washed thoroughly with water, then with alcohol and ether, and dried on a porous plate. When pure it was not readily discolored by the light.

The alkylations were carried out as already described.⁴ In the case of the silver salt it was impossible to obtain any reaction constants, as the silver iodide seemed to coat the unchanged urazole salt, even when the tubes were shaken con-

¹ Ber. d. chem. Ges., **41**, 3225-3235.

² Am. Chem. J., **39**, 132.

³ *Ibid.*, **38**, 59.

⁴ Ber. d. chem. Ges., **41**, 5221.

tinuously during the alkylation. The experiments were carried out at 60°. ¹ The constants were calculated by the usual bimolecular equation.

Table I.—0.3 Wt. N Sodium Salt of Phenyl-2-methylurazole and 0.3 Vol. N Methyl Iodide at 60°. ²

<i>t</i> (hours).	A.	Total product.	Per cent. N-ester.	AK.	AK' N-deriv.	AK'' O-deriv.
1	0.307	0.1890	96.0	1.6	1.53	0.07
2	0.307	0.2399	98.3	1.8	1.77	0.03
3	0.307	0.2616	95.5	1.9	1.81	0.09
4	0.307	0.2627		1.9		

Table II.—0.3 Wt. N Silver Salt of Phenyl-2-methylurazole and 0.3 Vol. N Methyl Iodide at 60°.

<i>t</i> (hours).	A.	Total product.	Per cent. N-deriv.	Per cent. O-deriv.
8	0.307	0.0893	51.0	49.0
17.5	0.307	0.0913	52.3	47.7
24	0.307	0.0877	49.5	50.5
28	0.307	0.0935	51.7	48.3

Table III.—0.3 Wt. N Sodium Salt of Phenyl-2-methylurazole and 0.3 Vol. N Ethyl Iodide at 60°.

<i>t</i> (hours).	A.	Total product.	Per cent. N-ester.	AK.	AK' N-deriv.	AK'' O-deriv.
0.5	0.3285	0.0298	(100.1)	0.199	0.199	...
1	0.3285	0.0607	91.0	0.226	0.205	0.021
2	0.3285	0.0848	91.0	0.174	0.158	0.016
3	0.3285	0.1042	95.8	0.154	0.147	0.007
4	0.3285	0.1144	...	0.133	...	...

Table IV.—0.3 Wt. N Silver Salt of Phenyl-2-methylurazole and 0.3 Vol. N Ethyl Iodide at 60°.

<i>t</i> (hours).	A.	Total product.	Per cent. N-deriv.	Per cent. O-deriv.
10	0.3285	0.0595	11.1	88.9
17.5	0.3285	0.1168	11.0	89.0
23	0.3285	0.1161	10.1	89.9
48	0.3285	0.0960	13.3	86.7

The 1-phenyl-2,4-dimethylurazole obtained from the experiments with methyl iodide melted sharply at 96°, ³ while

¹ For description of the bath see Brunel: Diss., Johns Hopkins Univ., 1906.

² Ber. d. chem. Ges., **41**, 3231, 3232.

³ *Ibid.*, **21**, 1223; **35**, 1563. Am. Chem. J., **38**, 69.

the 1-phenyl-2-methyl-4-ethylurazole melted at $114^{\circ}.5$.¹ From these experiments we see that this sodium salt is less reactive than the sodium salt of 1-phenyl-4-methylurazole.² It gives, however, about the same ratio of esters. When we come to the silver salts we find that while with methyl iodide the ratio of esters is about the same, with ethyl iodide the silver phenyl-2-methylurazole gives much more oxygen ester than the corresponding silver 1-phenyl-4-methylurazole under the same conditions.² That the salts of 1-phenyl-2-methylurazole are less reactive is what might be expected from the work of Shadinger³ on the affinity constants of these acids, the salts of the stronger urazole acids having generally higher alkylation velocities. It has therefore been found that the 4,5-urazole group has a greater tendency to give oxygen derivatives than the 2,3-group.

ALKYLATIONS OF 1-PHENYL-2-METHYLURAZOLE WITH DIAZOMETHANE.

The ether used in this work was dried over sodium, the acetone and chloroform over fused calcium chloride and the alcohols over lime, and distilled. Diazomethane was made by the method of von Pechmann.⁴ The methylurethane, obtained by the reaction of methylamine on ethyl chlorcarbonate, was treated in ether solution with the gases evolved by the action of nitric acid on arsenious oxide in order to obtain the methylnitrosourethane. According to von Pechmann⁵ this substance, as well as the diazomethane, is extremely poisonous. I have found, however, that neither of these substances had any ill effect on the skin, and the diazomethane did not affect my breathing in any way. The alkylations were carried out as follows: One gram of 1-phenyl-2-methylurazole was dissolved in a measuring flask in 100 cc. of the solvent to be used. In the case of ether 0.65 gram was the maximum amount of urazole that could be dissolved. Of this solution 20 cc. were taken for each experiment. The

¹ Am. Chem. J., **38**, 76.

² *Loc. cit.*

³ Am. Chem. J., **39**, 126.

⁴ Ber. d. chem. Ges., **27**, 1888; **28**, 855, 1624; **29**, 2591; **30**, 646.

⁵ *Ibid.*, **27**, 1888.

diazomethane solution was made by pipetting 2 cc. of the methylnitrosourethane into a dry 250 cc. flask and adding 30 cc. of dry ether and 2.2 cc. of a 25 per cent. methyl alcohol solution of potassium hydroxide.¹ Then the ether and diazomethane were distilled over into a receiver containing a small amount of ether to absorb the diazomethane gas, which came over very rapidly at first. The diazomethane solution was then made up to 100 cc. Ten cc. of this solution were transferred to a dry extraction funnel and an excess of a standard ethereal iodine solution added. The excess of the iodine was titrated back with sodium thiosulphate solution, starch being used as an indicator. This gave the strength of the diazomethane solution in cc. of iodine.² From a curve, prepared on the basis of this, the amount of diazomethane solution equivalent to 0.2 gram 1-phenyl-2-methylurazole was calculated. Then one-fourth of this amount of diazomethane solution was pipetted into a 100 cc. bottle and sufficient ether to make the solution up to 30 cc. was added. In the next bottle one-half, in the next three-quarters, and in the last, one molecular equivalent of the diazo solution was made up to 30 cc. as above. Usually it took from 20 to 22 cc. of the diazo solution for 0.2 gram of 1-phenyl-2-methylurazole. Twenty cc. of the urazole solution described above was run beneath the ether by means of a pipette and the bottles were shaken. The yellow color of the solutions generally disappeared immediately in all of the bottles; but in some cases a slight yellow color remained in the bottle containing equimolecular amounts of the two solutions. The mixed solvents were then evaporated off, the residue was transferred to an extraction funnel by means of chloroform and then extracted several times with alkali to remove the unchanged acid. Finally the chloroform solution was carefully evaporated off below its boiling point in a weighed dish. After the ester had come to constant weight in a vacuum desiccator, it was

¹ Ber. d. chem. Ges., **28**, 855.

² Monats. Chem., **24**, 364. Wegscheider and Gehringer reported that they obtained twice the amount of ester calculated from the iodine used. This does not agree with my results. Careful experiments have generally shown that the ester formed and iodine used correspond, but there are in some cases apparent discrepancies.

transferred by means of chloroform or ethyl bromide to a small tube drawn out to a capillary at one end. The solvent was then evaporated down to one or two cc. and 5 cc. of a saturated alcoholic hydrochloric acid solution added, and the tube was sealed off. The tube, which had to be handled carefully, was heated 1 hour at 100° and was then cooled and opened. The contents, after being transferred to a separating funnel, were extracted with alkali. This removed the 1-phenyl-2-methylurazole resulting from the hydrolysis of the 1-phenyl-2-methyl-5-methoxyurazole or 1-phenyl-2-methyl-3-methoxyurazole. The chloroform was evaporated off in a weighed dish and the resulting nitrogen ester was weighed. The error of this method is about 3 per cent.¹

Experiment 1.—20 cc. ether solution containing 0.13 gram of 1-phenyl-2-methylurazole (0.034 vol. N) and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.00568	0.0200	0.0199	(99.5)	(0.5)
0.01136	0.0337	0.0309	91.7	8.3
0.01703				...
0.0227	0.1254	0.1136	90.6	9.4

Experiment 2.—20 cc. chloroform solution containing 0.25 gram 1-phenyl-2-methylurazole (0.0654 vol. N) and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0109	0.0928	0.0843	90.8	9.2
0.0218	0.1114	0.1049	94.0	6.0
0.0328	0.2759	0.2563	92.9	7.1
0.0437	0.2735	0.2535	92.7	7.3

Experiment 3.—20 cc. acetone solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0851	0.0764	90.0	10.0
0.0174	0.1850	0.1691	91.3	8.7
0.0261	0.1953	0.1757	89.6	10.4
0.0348	0.2150	0.1958	91.1	8.9

¹ Ber. d. chem. Ges., 41, 3223.

Experiment 4.—20 cc. ethyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0889	0.0844	94.9	5.1
0.0174	0.1762	0.1632	92.6	7.4
0.0261	0.1976	0.1841	93.1	6.9
0.0348	0.2036	0.1870	92.0	8.0

Experiment 5.—20 cc. ethyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 3 mols. (0.670 gram) sodium 1-phenyl-2-methylurazole and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0910	0.0836	91.8	8.2
0.0174	0.1661	0.1494	90.0	10.0
0.0261	0.2105	0.1904	90.5	9.5
0.0348	0.2190	0.1978	90.3	9.7

Experiment 6.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0676	0.0609	90.4	9.6
0.0174	0.1143	0.1031	90.2	9.8
0.0261	0.1538	0.1378	89.6	10.4
0.0348	0.2136	0.1905	89.2	10.8

Experiment 7.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 3 mols. (0.670 gram) sodium 1-phenyl-2-methylurazole, and 30 cc. ethereal diazomethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.1121	0.0989	88.3	11.7
0.0174	0.1822	0.1628	89.3	10.7
0.0261	0.1786	0.1584	88.7	11.3
0.0348				

Table V.

Solvent.	Per cent. <i>N</i> -ester.			
	0.25 mol. diazo- methane.	0.5 mol. diazo- methane.	0.75 mol. diazo- methane.	1 mol. diazo- methane.
Ether		91.7		90.6
Chloroform	90.8	(94.0)	92.9	92.7
Acetone	90.0	91.3	89.6	91.0
Ethyl alcohol	(94.9)	92.6	93.1	92.0
Ethyl alcohol and 3 mols. sodium salt	91.8	90.0	90.5	90.3
Methyl alcohol	90.4	90.2	89.6	89.2
Methyl alcohol and 3 mols. sodium salt	88.3	89.3	88.7	

The 1-phenyl-2,4-dimethylurazole from these experiments melted at 96° and a mixture of this ester and the ester made from sodium 1-phenyl-2-methylurazole and methyl iodide also melted at 96°.

ALKYLATIONS OF 1-PHENYL-2-METHYLURAZOLE WITH DIAZOETHANE.

The experiments with diazoethane were carried out in the same way as those with diazomethane. The diazoethane was made from ethylnitrosourethane as described by von Pechmann.¹

Experiment 1.—20 cc. acetone solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazoethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of <i>N</i> -ester.	Per cent. <i>N</i> -ester.	Per cent. <i>O</i> -ester.
0.0087	0.1054	0.0708	67.2	32.8
0.0174	0.1902	0.1302	68.4	31.6
0.0261	0.1048	0.0734	70.0	30.0
0.0348	0.2199	0.1505	68.4	31.6

Experiment 2.—20 cc. ethyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazoethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of <i>N</i> -ester.	Per cent. <i>N</i> -ester.	Per cent. <i>O</i> -ester.
0.0087	0.0741	0.0550	(74.2)	(25.8)
0.0174	0.1393	0.0923	(66.2)	(33.8)
0.0261	0.1730	0.1212	70.0	30.0
0.0348	0.1740	0.1227	70.5	29.5

¹ Ber. d. chem. Ges., **31**, 2643.

Experiment 3.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 N) and 30 cc. ethereal diazoethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0307	0.0212	69.0	31.0
0.0174	0.0727	0.0488	67.1	32.9
0.0261	0.0763	0.0522	68.4	31.6
0.0348	0.1030	0.0695	67.5	32.5

Experiment 4.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole and 3 mols. (0.670 gram) sodium 1-phenyl-2-methylurazole, and 30 cc. ethereal diazoethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0862	0.0552	64.0	36.0
0.0174	0.1208	0.0780	64.5	35.5
0.0261	0.1388	0.0864	62.3	37.7
0.0348	0.1707	0.1043	61.1	38.9

Experiment 5.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole and 3 mols. (0.47 gram) sodium iodide, and 30 cc. ethereal diazoethane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0330	0.0227	68.7	31.3
0.0174	0.0409	0.0275	67.2	32.8
0.0261	0.0563	0.0362	66.6	33.4
0.0348	0.0662	0.0452	68.3	31.7

Table VI.

Solvent.	Per cent. N-ester.			
	0.25 mol. diazo- ethane.	0.5 mol. diazo- ethane.	0.75 mol. diazo- ethane.	1 mol. diazo- ethane.
Acetone	67.2	68.4	70.0	68.4
Ethyl alcohol			70.0	70.5
Methyl alcohol	69.0	67.1	68.4	67.5
Methyl alcohol and sod- ium salt	64.0	64.5	62.3	61.1
Methyl alcohol and sod- ium iodide	68.7	67.2	66.6	68.3

The 1-phenyl-2-methyl-4-ethylurazole melted at $114^{\circ}.5^1$

¹ Am. Chem. J., 38, 76, and page 18 in this article.

and was identical with the ester obtained from sodium 1-phenyl-2-methylurazole and ethyl iodide.

ALKYLATIONS OF 1-PHENYL-2-METHYLURAZOLE WITH DIAZOPROPANE.

Propylurethane was made from ethyl chlorcarbonate and propylamine. A one-liter separating funnel was half filled with water and 9.5 grams ethyl chlorcarbonate dissolved in 100 cc. ether were added. Five grams of propylamine diluted with ether were poured in slowly with frequent shaking and then small amounts of caustic potash solution were added, until the water remained alkaline after vigorous shaking. The ether solution was separated, dried, and evaporated and the propylurethane was distilled. It is a colorless liquid boiling at $191^{\circ}.5$ – $192^{\circ}.5$ under a pressure of 758 mm. The yield was 7 grams, or 72 per cent. of the theoretical. Analysis: 0.3625 gram substance gave 34.68 cc. nitrogen at 762.25 mm. and 27° .

	Calculated for $C_6H_{13}O_2N$.	Found.
N	10.68	10.56

Propylnitrosourethane was obtained by passing nitrous anhydride into an ethereal solution of propylurethane until it became dark green. The ethereal solution was then washed several times with water, then with sodium carbonate solution, and dried, and the ether was distilled off. The propylnitrosourethane was distilled in a vacuum. It is a reddish oil and resembles methylnitrosourethane in all its properties. From 5.8 grams of propylurethane 4.3 grams, or 70 per cent. of the theoretical yield, of a product boiling at 94° (uncorr.) under a pressure of 35 mm., were obtained. Analysis:

0.1239 gram substance gave 20.5 cc. nitrogen at 768.54 mm. and 27° .

	Calculated for $C_6H_{12}O_3N_2$.	Found.
N	17.50	18.15

The solution of diazopropane was made in the usual way from propylnitrosourethane and alcoholic potassium hy-

dioxide. It did not distil over as readily as the diazoethane and the ether solution was a deep yellow-brown. It seemed to react as rapidly as diazomethane and -ethane.

Experiment 1.—20 cc. acetone solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazopropane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087				
0.0174	0.1183	0.0819	69.2	30.8
0.0261	0.1733	0.1190	68.7	31.3
0.0348	0.2257	0.1558	69.0	31.0

Experiment 2.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazopropane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.1063	0.0628	59.1	40.9
0.0174	0.1067	0.0635	59.5	40.5
0.0261	0.1148	0.0657	57.2	42.8
0.0261	0.1186	0.0715	60.3	39.7
0.0348	0.1080	0.0643	58.6	41.4
0.0348	0.1370	0.0824	60.1	39.9
0.0348	0.1078	0.0629	58.3	41.7

Table VII.

Solvent.	Per cent. N-ester.			
	0.25 mol. diazo- propane.	0.5 mol. diazo- propane.	0.75 mol. diazo- propane.	1 mol. diazo- propane.
Acetone		69.2	68.7	69.0
Methyl alcohol	59.1	59.5	58.8 ¹	59.0 ²

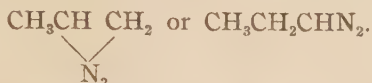
The 1-phenyl-2-methyl-4-propylurazole melted at 81°–82° and was in every way identical with the ester obtained from sodium 1-phenyl-2-methylurazole and *n*-propyl iodide.³ This is especially interesting since I have thus eliminated the

¹ Average of two ratios.

² Average of three ratios.

³ See page 18.

possibility of obtaining an isopropyl ester also. For diazopropane may have the structure



If the first formula were correct we would expect, from the general behavior of such compounds, some isopropyl ester to be formed.

ALKYLATIONS OF 1-PHENYL-2-METHYLURAZOLE WITH DIAZOBUTANE.

Butylurethane was made in exactly the same way as propylurethane. It is a colorless liquid boiling at $208^\circ\text{--}211^\circ$ (uncorr.) at 770 mm. From 6 grams butylamine 10 grams pure product, or 83 per cent. of the theoretical yield, were obtained.

Butylnitrosourethane was also made in the same way as propylnitrosourethane. It was more viscous than the propyl compound and could not be distilled even in a vacuum; consequently no further attempt was made to purify it. It decomposed violently at its boiling point.

The diazobutane made from the unpurified butylnitrosourethane was similar to the diazo compounds described before. It evidently is a liquid boiling at a slightly higher temperature than ether, for it did not begin to distil over until most of the ether had already collected in the receiver. The solution was somewhat darker in color than the diazopropane solution. It did not seem to have as disagreeable an odor as diazomethane.

Experiment 1.—20 cc. acetone solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazobutane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of <i>N</i> -ester.	Per cent. <i>N</i> -ester.	Per cent. <i>O</i> -ester.
0.0087	0.0934	0.0597	63.9	36.1
0.0174	0.2048			
0.0261	0.2379	0.1508	63.4	36.6
0.0348	0.2421	0.1537	63.5	36.5
0.0348	0.2326	0.1489	63.9	36.1
0.0348	0.2259	0.1430	63.3	36.6
0.0348	0.2090	0.1319	63.1	36.9

Experiment 2.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 vol. N) and 30 cc. ethereal diazobutane solution.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087	0.0352	0.0190	54.0	46.0
0.0174	0.0740	0.0402	54.3	45.7
0.0261	0.0948	0.0510	53.8	46.2
0.0348	0.1587	0.0889	56.0	44.0
0.0348	0.1933	0.1072	55.4	44.5

Table VIII.

Solvent.	Per cent. N-ester.			
	0.25 mol. diazo- butane.	0.5 mol. diazo- butane.	0.75 mol. diazo- butane.	1 mol. diazo- butane.
Acetone	63.9	63.4	63.5	63.4 ¹
Methyl alcohol	54.0	54.3	53.8	55.7 ²

The 1-phenyl-2-methyl-4-butylurazole was obtained as an oil which did not crystallize. The compound made from the sodium salt and butyl iodide is also an oil.³

ALKYLATIONS OF 1-PHENYL-2-METHYLURAZOLE WITH DIAZO-PROPYLENE.

Allylurethane was made in the usual way from allylamine and ethyl chlorcarbonate. From 5 grams of allylamine, 7.5 grams of a colorless oil boiling at 194°.5–195° (uncorr.) under a pressure of 768 mm. were obtained. Yield, 66 per cent. of the theoretical. Analysis:

0.2487 gram substance gave 24.60 cc. nitrogen at 24° and 755.8 mm.

	Calculated for C ₆ H ₁₁ O ₂ N.	Found.
N	10.85	11.00

Allylnitrosourethane was made in the same way as the other nitrosourethanes. It is a reddish oil which decomposes when distilled in a vacuum and so no attempt was made to purify it by distillation.

The ether solution of diazopropylene had a deep wine color instead of the usual yellow color of the other diazo solutions.

¹ Average from four experiments.

² Average from two experiments.

³ See page 18.

The diazopropylene acted on the 1-phenyl-2-methylurazole very slowly, several hours being necessary to discharge the color completely. The amount of ester formed in any one case was very small, as the following experiments show:

Experiment 1.—20 cc. methyl alcohol solution containing 0.20 gram 1-phenyl-2-methylurazole (0.0523 volume N) and 30 cc. of ethereal diazopropylene.

Conc. diazo sol. Vol. N.	Weight of total product.	Weight of N-ester.	Per cent. N-ester.	Per cent. O-ester.
0.0087				
0.0174	0.0288	0.0194	67.3	32.7
0.0261	0.0368	0.0246	66.8	33.2
0.0348	0.0135	0.0091	67.4	32.6
0.0348	0.0120	0.0079	65.8	34.2

The 1-phenyl-2-methyl-4-allylurazole melts at 61°–64°. The compound was obtained also by the action of allyl iodide on the sodium salt of 1-phenyl-2-methylurazole in alcoholic solution. It melted after crystallization from alcohol at 62°–64° and at 61°–64° when mixed with a sample obtained in the above experiment.

Table IX.—Summary of Experiments in Methyl Alcohol-Ether.

Diazoalkyl.	Per cent. N-ester.			
	0.25 mol. diazo- alkyl.	0.5 mol. diazo- alkyl.	0.75 mol. diazo- alkyl.	1 mol. diazo alkyl.
Diazomethane	90.4	90.2	89.6	89.2
Diazoethane	69.0	67.1	68.4	67.5
Diazoethane + sodium salt	64.0	64.5	52.3	61.1
Diazoethane + sodium iodide	68.7	67.2	66.6	68.3
Diazopropane	59.1	59.5	58.8 ¹	59.0 ¹
Diazobutane	54.0	54.3	53.8	55.7 ¹
Diazopropylene		67.3	66.8	66.6 ¹

Table X.—Summary of Experiments in Acetone-Ether.

Diazoalkyl.	Per cent. N-ester.			
	0.25 mol. diazo- alkyl.	0.5 mol. diazo- alkyl.	0.75 mol. diazo- alkyl.	1 mol. diazo- alkyl.
Diazomethane	90.0	91.3	89.6	91.1
Diazoethane	67.2	68.4	70.0	68.4
Diazopropane		69.2	68.7	69.0
Diazobutane	63.9		63.4	63.4 ²

¹ Average from two or more experiments.

² Average of two or more ratios.

Table XI.—Summary of Experiments in Ethyl Alcohol-Ether.

Diazoalkyl.	Per cent. N-ester.			
	0.25 mol. diazo- alkyl.	0.5 mol. diazo- alkyl.	0.75 mol. diazo- alkyl.	1 mol. diazo- alkyl.
Diazomethane	94.9	92.6	93.1	92.0
Diazomethane + sodium salt	91.8	90.0	90.5	90.3
Diazoethane			70.0	70.5

Table XII.—Summary of Experiments in Chloroform-Ether.

Diazoalkyl.	Per cent. N-ester.			
	0.25 mol. diazo- alkyl.	0.5 mol. diazo- alkyl.	0.75 mol. diazo- alkyl.	1 mol. diazo- alkyl.
Diazomethane	90.8	94.0	92.9	92.7

Table XIII.—Summary of Experiments in Ether-Ether.

Diazoalkyl.	Per cent. N-ester.			
	0.25 mol. diazo- alkyl.	0.5 mol. diazo- alkyl.	0.75 mol. diazo- alkyl.	1 mol. diazo- alkyl.
Diazomethane		91.7		90.6

The above tables show conclusively that constant ratios are obtained for varying amounts of diazoalkyl. The maximum variation in any one series is not over 5 per cent. and the average variation is only about 1.5 per cent., or well within the limit of experimental error. Another fact that is noticed at once is the increase in the amount of oxygen ester with increase in weight of the alkyl group. When we change from diazomethane to diazoethane, in the methyl alcohol solutions, we have a change of 20 per cent. in the ratio of esters, a change of 10 per cent. when we change from diazoethane to diazopropane, and then only a change of 5 per cent. when diazobutane is used. In the experiments in acetone there is about the same difference in the diazomethane and -ethane series. It seems peculiar that here diazoethane and -propane should give about the same ratios. There is, however, a drop of about 5 per cent. in the ratios obtained when diazobutane is used instead of diazopropane. Taken all together, the experiments show conclusively that, as rapid as the alkylations are, K_3 is established so rapidly that it need not be considered to vary with different time periods.

CONCLUSIONS.

1. The conditions affecting the constancy of the ratio of products obtained from a tautomeric substance have been discussed.

2. 1-Phenyl-2-methylurazole has been alkylated with varying molecular proportions of different diazoalkyls and in all cases, for any one series of experiments, a constant ratio of esters has been obtained. This shows conclusively that the constants for the velocity of rearrangement of the two forms of 1-phenyl-2-methylurazole are very large in comparison with K_{trans} and K'_{trans} , or, in other words, K_3 is maintained constant during the alkylation.

3. 1-Phenyl-2-methylurazole and a given diazoalkyl give different ratios of esters in different solvents.

4. 1-Phenyl-2-methylurazole and different diazoalkyls give different ratios of esters in the same solvent.

5. Evidence has been given to show how we may have abnormal hydrolysis of the sodium salt of 1-phenyl-2-methylurazole. In the presence of sodium 1-phenyl-2-methylurazole the 1-phenyl-2-methylurazole gives with diazomethane and with diazoethane ratios of esters which are different from the ratios obtained when no sodium salt is present. This leads to the conclusion that the equilibrium point of the two (or more) tautomeric forms of the sodium salt may be different from that of the two tautomeric forms of the acid, and hence gives a possible explanation of abnormal hydrolysis. These conclusions have been further strengthened by the work of Mr. E. K. Marshall, who has attacked this problem by more direct methods.

On the Rearrangement of the Tautomeric Salts of 1,4-Diphenyl-5-Thionurazole and 1,4-Diphenyl-5-Thiolurazole.

THEORETICAL.

Tautomeric compounds may be roughly classified under two heads;¹ first, those in which the equilibrium between the different forms is established very quickly in comparison with the velocity of the particular reaction being studied, and, second, those in which the equilibrium is established at a rate comparable with that of the reaction. The ideas of tautomeric equilibrium and especially of tautomeric salts, advanced by Acree² and collaborators, have made possible the quantitative study of the first case with results entirely in harmony with the theory. While the slow rearrangement of tautomeric acids and their final states of equilibrium have been measured by several investigators, no quantitative work has been done on the tautomeric salts of such acids, especially in the light of the theory of Acree. Such work should give a severe test for this idea and the results should be conclusive one way or the other. The most important work

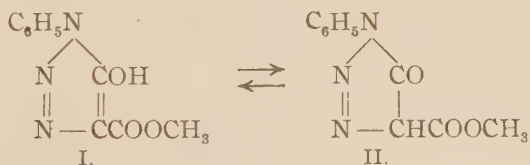
¹ Am. Chem. Jour., **43**, 361, 424.

² *Ibid.*, **37**, 71; **38**, 1; **39**, 124, 226. Ber. d. chem. Ges., **41**, 3199.

along this line has been done by Wislicenus,¹ Dimroth,² and Michael.³

Wislicenus, working on formylphenylacetic ester, was able to isolate a liquid enol and a solid keto form,⁴ and to measure roughly the equilibrium between the two in a number of cases. He found that nondissociating solvents were favorable to that form which he called the enol or weaker acid form. The greater the concentration the more enol form he found in the solution. Starting with either form, under the same conditions of temperature and concentration, he found that the solutions are the same at the end of the reaction, thus showing that the rearrangement is perfectly reversible. His work on the salts was not very conclusive. The sodium salt made from either form liberated the so-called enol ester when precipitated with carbon dioxide, while with sulphuric acid the keto ester was liberated. Two different copper salts were also made but their exact constitution is doubtful.

The work of Dimroth⁵ on methyl 1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylate was more conclusive owing to the fact that both tautomeric forms are stable solids, which in solution attain the following equilibrium:



The enol form (I) is a strong acid and liberates iodine quantitatively from potassium iodate and iodide in acid solution, while the keto form (II) is practically neutral. Dimroth found that the amount of the strongly acid enol form was greatest in the strongly dissociating solvents, this being in harmony with Wislicenus' results. In water, for example, the ratio of enol to keto is 1 : 14, in methyl alcohol 1 : 150,

¹ Ann. Chem. (Liebig), **291**, 147. Abrens' Sammlung, II, 186.

² Ann. Chem. (Liebig), **335**, 1; **338**, 143.

³ Michael and Hibbert: Ber. d. chem. Ges., **41**, 1080.

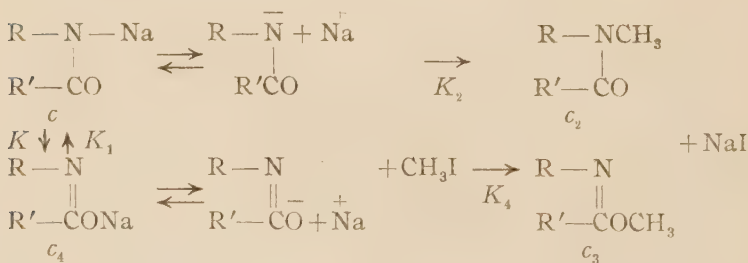
⁴ This was afterwards shown by him, and also by Michael, to be a mixture.

⁵ Loc. cit.

in ethyl alcohol 1:300, while in chloroform, ether, etc., only the merest trace of enol form was found. An interesting fact observed was that the equilibrium was independent of temperature and concentration. In regard to the rate of rearrangement it was found that the change of the enol into the keto form was greatest in nonaqueous solvents, showing that the reaction was not due to the addition and splitting out of water. The molecular forms of the acids and not the anions were thought to be in direct equilibrium, as was also thought by Acree¹ to be true in the case of the salts of the urazoles, although the evidence for this is very meagre. No work could be done with the salts, as the keto ester is practically a nonelectrolyte and does not form stable salts.

Michael and Hibbert came to the conclusion that there is no direct connection between the equilibrium point, or velocity of change, of two tautomers and the physical constants of the solvents, such as the dielectric constant.

As we see, the work of Wislicenus, Dimroth, and Michael and Hibbert was concerned simply with the study of the rate of rearrangement and equilibrium of the acids themselves, and no attempt was made to study quantitatively and systematically the action of alkylating agents or other substances on either of the acids or their salts, or on an equilibrium mixture of the two. This is not a simple problem, as is shown by the following considerations:



In this scheme c is the original concentration of the keto form, c_4 that of the enol form, c_1 the amount of keto salt trans-

¹ *Am. Chem. Jour.*, **38**, 1. Wegscheider: *Z. physik. Chem.*, **35**, 518; **36**, 543. Goldschmidt: *Z. Elek. Chem.*, **11**, 5. Dimroth: *Ibid.*, **11**, 137.

formed into enol, c_2 the concentration of the keto ester, and c_3 that of the enol ester. Taking the simplest case first, suppose an equimolecular amount of methyl iodide is added to a solution containing a mixture of the two salts. We would have the following three reactions taking place:

(a) Sodium keto salt $\rightleftharpoons$ sodium enol salt.

(b) Sodium keto salt and $\text{CH}_3\text{I} \longrightarrow$ methyl keto ester and NaI .

(c) Sodium enol salt and $\text{CH}_3\text{I} \longrightarrow$ methyl enol ester and NaI .

These would be represented by the differential equations:

$$\frac{dc_1}{dt} = K(C - C_1 - C_2) - K_1(C_4 + C_1 - C_3)$$

$$\frac{dc_2}{dt} = K_2(C - C_1 - C_2)(C + C_4 - C_2 - C_3)$$

$$\frac{dc_3}{dt} = K_4(C_4 + C_1 - C_3)(C + C_4 - C_2 - C_3)$$

In these equations K is the velocity constant for the change of keto salt into enol salt, K_1 the constant for the reverse rearrangement, K_2 that for the formation of keto ester, and K_4 that for the formation of enol ester. The integration of these three equations would give a complete solution of the problem. This was not attempted, as the simultaneous alkylation and rearrangement was not studied. The differential equations for the case in which the salt rearrangement is not reversible, as well as for those in which the esters rearrange, have been worked out, but as they were not used in the work reported now, they will not be given. The above equations do not take into consideration the question whether the rearrangements or the alkylation reactions of the two tautomeric salts are ionic, or molecular, or both, side by side. If, however, the principle of isohydric solutions holds, the ratio of the concentration of the anions to that of the molecular salt should not change appreciably for either of the two forms in the solution, as we have sodium iodide formed in an amount equivalent to the sum of the keto

and enol salts disappearing by esterification. Then the different constants used above would equal the real reaction constants multiplied by α or $1-\alpha$, according as the reactions are ionic or molecular or both, where α is the percentage of ionization. Then, for example, $K = (1 - \alpha) K'$, $K_1 = \alpha K'_1$, or $K_2 = K'_2 \alpha + K''_2 (1 - \alpha)$, when K' , K'_1 , K'_2 and K''_2 are the true constants.

It is assumed that the rearrangement of the salt is a monomolecular reaction, as that seems to be made most probable by my work, described below, and that of Mr. E. P. Doetsch. The possibility, however, that the rearrangement is due to a union of the ions in the solution with the molecular form of the salt, or to other complex reactions, is not excluded, and this possibility is being investigated. In this case the rearrangement would not be monomolecular, although in some cases it might still apparently be so.¹

The study of the slow attainment of equilibrium between the two forms of a weakly acid tautomeric substance should give most conclusive evidence as to the question of abnormal hydrolysis in the more concentrated solutions.² If we should add a solution containing an equilibrium mixture of the sodium salts, for example, to a solution of an equilibrium mixture of the free acids, we could easily calculate the total amount of each form in the solution, provided there was no abnormal hydrolysis. We could in some cases use conductivity methods. In other cases the whole mixture could be alkylated very quickly and the ratio of esters determined. If we have abnormal hydrolysis, the calculated should differ from the experimental values by an amount depending on the difference between the affinity constants of the two forms, the equilibrium constants, etc. The possibility of the influence of double salts, complex molecules, solvates, etc., must be carefully considered.

The compounds that first suggested themselves as being easily obtainable for my work were Dimroth's two forms³

¹ Acree and Nirdlinger: *Am. Chem. Jour.*, **43**, 358. Julius Meyer: *Z. physik. Chem.*, **66**, 81; **67**, 257.

² *Am. Chem. Jour.*, **43**, 365.

³ *Ann. Chem. (Liebig)*, **335**, 1.

of methyl 1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylate. The enol form is a strong acid while the keto form is practically neutral. This would make it necessary, in esterifying a mixture of the two forms, to separate the keto form from the neutral ester formed, by converting it into the enol and extracting with an alkali. It was found that by rapid work the enol acid could be easily extracted from chloroform or ethereal solutions by means of aqueous solutions of potassium hydroxide, and the keto acid could be easily converted into the enol acid and extracted by treating the mixture with alcoholic solutions of potassium hydroxide. When the methyl enol ester, however, was treated by this method it was saponified to a considerable extent. For example, 0.1282 gram keto form and 0.1065 gram methyl enol ester were dissolved in chloroform, the chloroform evaporated, and the residue taken up in alcoholic potash. Then water was added and the solution extracted with chloroform and only 0.2 milligram of extracted substance was obtained. In another case from 0.1870 gram ester only 0.0059 gram of extract was obtained. In still another case in which the solutions were carefully cooled 0.1011 gram ester gave back 0.0672 gram unchanged ester. On this account the work had to be given up.

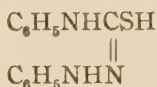
The compounds finally chosen for this work were the 1,4-diphenyl-5-thionurazole and 1,4-diphenyl-5-thiolurazole first described by Marckwald¹ and later by Busch² and his collaborators. A short summary of the evidence for the constitution of these compounds is necessary as my work has shown that the constitutions previously given are wrong. I should like to state at once that the work with these 5-thiourazoles is much more difficult than any that I have yet done. The properties of the compounds do not allow the development of very accurate quantitative methods, and added complications, due to the tautomeric changes going on, make the slow progress of the work sometimes very discouraging. Since these are the very phase of tautomerism that I wish

¹ Ber. d. chem. Ges., **25**, 3098; **29**, 2920.

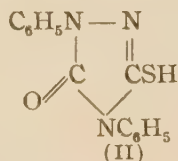
² Holzmann: Diss., Erlangen, 1902.

now to study, however, I shall continue the investigation of the problem.

W. Marckwald¹ found that by the action of phenylhydrazine on phenyl mustard oil in the cold, an α -diphenylthiosemicarbazide was formed which melted at 139° and then rearranged into the β -semicarbazide melting at 176° described by E. Fischer.² Marckwald gave to this α -semicarbazide formula (I) and the constitution of the thiourazole formed



(I)



(II)

by treating this with phosgene in the cold was thought to be represented by formula (II). This urazole melted at 219° – 221° when crystallized from *hot* alcohol, and when treated with methyl iodide yielded an ester melting at 185° (196° is the true melting point.) This ester gave methyl sulphhydrate and the salt of 1,4-diphenylurazole when it was treated with potassium hydroxide, a reaction which showed that the methyl is attached to the sulphur atom. These points, especially the crystallization from *hot* alcohol, which causes a rearrangement, should be noted, as they are of considerable importance.

In the first papers³ by Acree on the urazoles, it was stated that work was in progress on the 3-thio (or hydroxy)-5-hydroxy (or thio) urazoles, but this was stopped at that time in favor of Professor Busch. But the evidence which Acree⁴ obtained proved beyond question that Marckwald's formulation for the constitution of the α - and β -thiosemicarbazides and the above-mentioned thiourazoles was wrong. It was proved that the α -1-phenylmethylthiosemicarbazide assumed by

¹ *Loc. cit.*

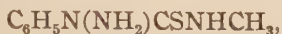
² *Ann. Chem. (Liebig)*, **190**, 122.

³ *Am. Chem. Jour.*, **27**, 126. *Ber. d. chem. Ges.*, **35**, 556; **36**, 3139.

⁴ The work which I have done since 1901 on these thiourazoles will be published soon. Professor Busch has in the meantime done far more, and better, work on these substances and cleared up beautifully some of the questions which are of great importance in this series of tautomeric substances.

S. F. ACREE.

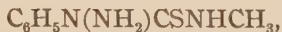
Marckwald to be the 1,4 compound, must be the 2,4 compound and have the formula



and that it rearranges, when heated in alcohol, especially in the presence of acids,¹ into the 1,4 compound having the formula



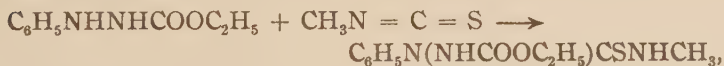
The proof, which was clear-cut, is the following: The α compound,



when heated with ethyl chlorcarbonate in chloroform solutions, with or without sufficient sodium bicarbonate to neutralize the hydrochloric acid liberated, gave the ester



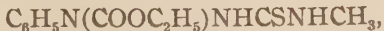
which, when treated with alkalis and then with an acid, yielded the 1-phenyl-4-methyl-3-hydroxy-5-thiourazole (A), which melted at 208°. This same ester was furthermore made by a reaction which could leave no doubt as to its constitution, namely, by the action of methyl mustard oil on phenyl carbazinic ester,



and when treated with alkalis as above it gave the same 1-phenyl-4-methyl-3-hydroxy-5-thiourazole, melting at 208°. But the β -phenylmethylthiosemicarbazide,

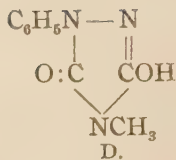
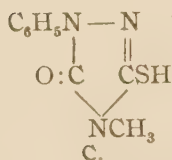
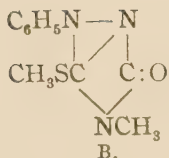
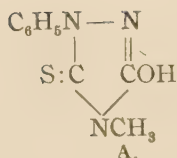


and ethyl chlorcarbonate in chloroform solution gave an isomeric ester,

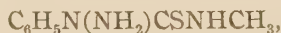


which, when treated with alkalis, etc., yielded an *isomeric* 1-phenyl-4-methyl-3-thiourazole (C), melting at 185°, which was also synthesized by an independent method.

¹ Ber. d. chem. Ges., 25, 3098. I ask that the study of this and similar rearrangements be left to me.



These two isomeric urazoles, (A) and (C), had therefore been synthesized by methods which could leave no doubt as to their constitution, or that the α -semicarbazide is the 2,4-phenylmethyl-3-thiosemicarbazide,



and that the β -semicarbazide is the 1,4-phenyl-3-thiosemicarbazide,



instead of the stereoisomeric forms of the 1,4-phenylmethyl-3-thiosemicarbazide as assumed by Marckwald.

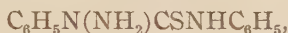
Furthermore, a comparison of the properties of Acree's two isomeric 1-phenyl-4-methylthiourazoles left no doubt that Marckwald's 1,4-diphenylthiourazole melting at 221° was *not* a 3-thio compound, as assumed by him, but a 5-thio compound analogous to the 1-phenyl-4-methyl-5-thiourazole. The esters obtained by alkylating the 1-phenyl-4-methyl-5-thiourazole were certainly partially 5-thio alkyl compounds (B), because they gave a considerable quantity of 1-phenyl-4-methylurazole (D) and alkyl sulphhydrates when warmed with acid or alkaline solutions. They were therefore in every respect analogous to Marckwald's methyl ester melting at 184° (analogous to B), which he thought to be a 3-thiol methyl ester. That Marckwald's methyl thiol ester could not be a 3-thiol ester was further clear from the fact that of a large number of 3-thiol esters synthesized by Acree¹ by methods

¹ Ber. d. chem. Ges., **36**, 3139.

which left no doubt as to their constitution, not one lost the alkyl sulphhydrate group to any appreciable extent when simply warmed with alkalis, these compounds being particularly stable towards alkaline reagents.

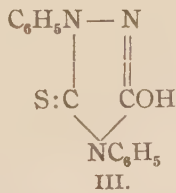
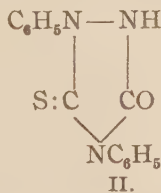
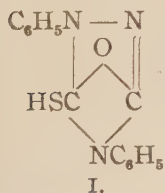
The evidence obtained by Acree shows conclusively then that Marckwald's so-called stereoisomeric thiosemicarbazides are the structurally isomeric 2,4- and 1,4-dialkyl-3-thiosemicarbazides, and that his so-called 1,4-diphenyl-3-thiourazole is in reality a 1,4-diphenyl-5-thiourazole.

But Busch¹ and Holzmann, in by far the best work then done on this problem, also came to the conclusion that the low-melting α -semicarbazide has the constitution



which is, chiefly because of their work, generally accepted to-day.

These chemists and other coworkers obtained by the action of phosgene on the α -diphenylthiosemicarbazide, a urazole acid which they supposed to be a 5-thiourazole² (I). It melted, without further treatment, at 141° , and at this temperature, or on recrystallization from hot alcohol, rearranged into another form, which they assumed to have the constitution (II) or (III), or to be perhaps an equilibrium mixture of the two. This substance melted at 219° – 221° , the fusion point of the compound obtained by Marckwald.



Busch and his colleagues believed that the low-melting urazole is a thiourazole (I), because it yielded, when treated with methylating agents, the methyl thiol ester (IV), which

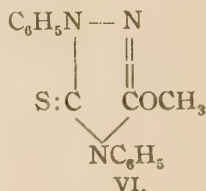
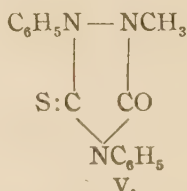
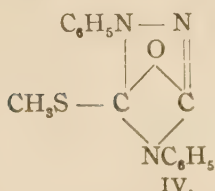
¹ Ber. d. chem. Ges., **34**, 326.

² See Ber. d. chem. Ges., **25**, 3098; **34**, 326, 340; **35**, 974. Holzmann: Diss., Erlangen, 1902. Grohmann: *Ibid.*, 1900. Reinhardt: *Ibid.*, 1906. Illgen: Dissertation, Berlin, 1894.

lost methyl mercaptan easily when treated with potassium hydroxide. Furthermore, they obtained the same methyl thiol ester, having undoubtedly this constitution, by treating the thiomethyl- α -semicarbazide,



with phosgene.



Reinhardt proved that the two forms of the acid give different sodium salts. He tried to methylate the two salts with methyl iodide, but heated the reaction mixture to 100° in a sealed tube and, as a result, in both cases he obtained an ester, melting at 137° , free from sulphur, of 1,4-diphenylurazole. He¹ found that on treating the sodium salt of the low-melting acid with dimethyl sulphate, an oily mixture was obtained. This is an important observation and should be kept in mind. The sodium salt of the high-melting acid, which he thought to have the constitution (II) or (III), gave with dimethyl sulphate the ester before mentioned melting at 196° and known to have the constitution (IV), corresponding to the urazole (I). He explained this discrepancy by stating that, on account of the vigorous action of the dimethyl sulphate the acid of formula (II) is transformed into (I), which is more easily methylated. The silver salt of the acid melting at 141° , when treated with methyl iodide,² gave an oil which was not easily crystallized. The silver salt of the acid melting at 221° , supposed to have the constitution (II), under the same conditions gave (1) a small amount of an ester melting at 133° – 134° , which did not split out mercaptan, and (2) much of the methyl thiol ester melting at 196° . This was also explained on the assumption that the silver is bound

¹ *Loc. cit.*, p. 72.

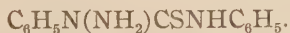
² *Loc. cit.*, p. 77.

partly to the sulphur, or that in the salt formation, some salt of the more reactive acid (I) was formed.

The work¹ described in the following pages was started provisionally on Busch's assumption that the low-melting acid has the composition (I) and the high-melting compound the composition (II). I was, however, soon forced to the conclusion that the low-melting acid is in reality 1,4-diphenyl-5-thionurazole, which can exist in two forms (II) and (III) in equilibrium, and that the high-melting form is a 1,4-diphenyl-5-thiolurazole, (I). This conclusion was reached for several reasons:

(1) In no case has the thiol methyl ester, (IV), corresponding to (I), been obtained from the pure low-melting acid, (II) or (III), in appreciable quantity. I have tested this point quantitatively and have never found more than 4 per cent. of this ester. The acid used by Marckwald,² which melted at 219°–221°, yielded a thiol methyl ester melting at 196°, and consequently was the form (I). My own work amply confirms this conclusion. In every case the low-melting acid, (II) or (III), has, on esterification, given an oily product. This would be expected if it were the 1,4-diphenyl-5-thionurazole, which can exist in two forms, (II) and (III), and consequently would be likely to give a mixture of N-ester and O-ester, (V) and (VI).

In the presence of the phosgene the 2,4-diphenyl-3-thiosemicarbazide would function as a base and would react chiefly as



This should act with phosgene like all substituted ammonias and give first chiefly



just as the phenylcarbazinic esters do when treated with

¹ After Dr. Nirdlinger's work was finished in June, 1909, and reported at the Detroit meeting of the American Chemical Society in July, 1909 (Slagle and Acree: *Am. Chem. Jour.*, **42**, 123), Professor Busch wrote me in the autumn of 1909 and stated later in *Ber. d. chem. Ges.*, **42**, 4763, that he now believes, on account of his recent work, his former views to be incorrect. He now advocates the formulas deduced from the work in the present communication as being correct.—S. F. A.

² *Ber. d. chem. Ges.*, **25**, 3098.

phosgene.¹ The group NHCOCl could now, as an acid chloride, react with the weakly basic NHC_6H_5 group, giving the 5-thionurazole:



The mechanism of the reaction by which the methyl ester of the 2,4-diphenyl-3-thiosemicarbazide gives the urazole methyl thiol ester (IV) when treated with phosgene² is not sufficiently clear to warrant any assumptions regarding the reaction. There is no doubt, however, that the urazole ester has the structure (IV).

(2) The high melting acid (I) gives the corresponding methyl thiol ester (IV), as would be expected if it had the structure (I) and not the thion structure (II) or (III), formerly assigned to it by Busch.³ Busch's idea that the presence of the methyl thiol ester (IV) is due to a reverse rearrangement of the real thion acid, (II) or (III), on salt formation, is not in harmony with my data. For if the thionurazole rearranges into the thiolurazole in the presence of an alkylating agent and gives a corresponding thiol ester, it is hard to understand why the low-melting form, which Busch supposed to be the thiolurazole, always gives an oily mixture of ester, and never a thiol ester; if the thionurazole rearranges into the thiol acid and gives a thiol ester, the low-melting acid supposed by Busch to be a thiolurazole form should give this ester all the more readily.

(3) When the low-melting urazole, which when pure yields no thiol ester, is partially transformed, as indicated by a change in melting point, by heat or otherwise, into the high-melting acid, the resulting mixture yields on alkylation with alkalis and methyl iodide varying amounts of methyl thiol ester and less thion ester, depending upon the extent of the rearrangement.

¹ Heinrichs: Diss., Erlangen, 1900.

² Marckwald: *loc. cit.*; Busch and Holzmann: Ber. d. chem. Ges., **34**, 340.

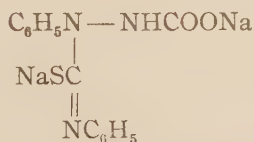
³ Ber. d. chem. Ges., **34**, 326.

(4) The work of Doctors Brunel, Johnson, Shadinger, Rogers and Nirdlinger shows that the salts of the 3-thiourazoles react with alkyl halides many times as rapidly as the corresponding 3-hydroxy salts, practically pure thiol esters being formed. Using this as a diagnosis, we are forced again to the conclusion that the high-melting urazole (225°) is the 5-thiol form, (I), and the low-melting form (141°) is the 5-thion compound, (II) or (III). The sodium salt of the high-melting urazole (225°) reacts, in alcoholic solutions of methyl iodide, about 80 times as rapidly as does the sodium salt of the low-melting form (141°). This is shown quantitatively on pages 55-57.

The only point not worked out yet is the fact that the carbethoxy ester,



gives the high-melting form on treatment with an alkali,¹ while it might give the low-melting acid. Unfortunately I have not been able recently to secure this ester again in order to saponify it *in the cold* with alkalies and learn whether the urazole acid formed is really a pure thiolurazole or a mixture of the two urazoles with the melting point of the thiolurazole, 225° (see p. 52). When we consider, however, the grouping $\text{R}(\text{CS})\text{NHC}_6\text{H}_5$ we see that in the presence of an alkali we could have part of the metal attached to the sulphur. The ester would be saponified and could give



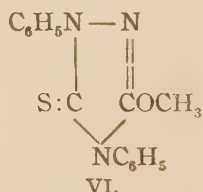
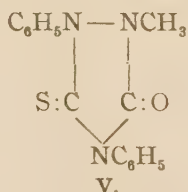
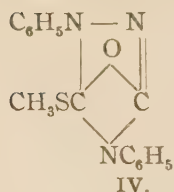
which could, on addition of an acid, split out water and change partly into the corresponding thiol acid, just as the methyl ester of the α -semicarbazide does when treated with phosphoric acid.

In order to show that certain samples of these acids give their own separate esters I give the following as an exam-

¹ Grohmann: Diss., Erlangen, 1900, p. 15.

ple: The sodium salt from 0.202 gram of the low-melting acid gave 0.2022 gram methyl ester which contained only 0.0088 gram of methyl thiol ester, while the sodium salt from 0.202 gram of the high-melting urazole acid gave 0.1843 gram of methyl ester which contained 0.1628 gram methyl thiol ester. This shows conclusively that this sample of low-melting acid gave practically no thiol ester, and that the high-melting acid gave practically all thiol ester. This is what we should expect if the low-melting acid is 1,4-diphenyl-5-thionurazole, (II) or (III), and the high-melting acid, 1,4-diphenyl-5-thiolurazole (I).

Knowing now the real constitution of these urazoles, let us consider what we should expect of them in the light of the theory of tautomeric salts. Firstly, we could expect each salt to give its own individual esters by a direct reaction. Then the pure sodium 1,4-diphenyl-5-thionurazole could, and does, give on alkylation with methyl iodide a mixture of the N- and O-esters, (V) and (VI), just as 1-phenyl-4-methylurazole yields the two corresponding N- and O-esters:



In solution, however, the sodium 1,4-diphenyl-5-thionurazole could, and does, rearrange slowly into sodium 1,4-diphenyl-5-thiolurazole, which gives the methyl ester (IV). This ester, which contains the SCH₃ group, should be, and is, very different from the two esters mentioned above, and can be separated quantitatively from them. My problem then is to apply the proper equations to these reactions and determine whether we get constants as demanded by the theory. Whether we should use one equation or another depends on whether the rearrangement of the salts is reversible or not. Since it is not practicable to measure directly the ratio of the two salts in solution by conductivity or analogous methods, and

since the salts cannot be easily isolated from mixtures, the solution of the problem depends on the formation of stable derivatives from the two salts, the ratio of which can be measured. If we start with an individual salt, the problem would be to determine at any moment the ratio of thion to thiol ester formed. If, therefore, K and K_1 (see page 37) are much smaller than the reaction constants (K_2 and K_4) of any alkylating agent, it would be only necessary to determine K and K_1 independently by adding, for instance, a large excess of alkylating agent to a solution of the salt after any time period, and measuring the ratio of esters formed. In the same way, K_2 and K_4 could be determined independently by alkylating the pure salts under conditions such that there would be no appreciable rearrangement of these salts. In the case of these thiourazoles we have such conditions and this method can be used in all ordinary reactions of these compounds. Some alkylating agents, however, may be found, such that K , K_1 , K_2 and K_4 will have nearly equal values, when the integrals of the general equations given on page 37 can be used.

If accurate analytical methods can be developed for studying these tautomeric 5-thion- and 5-thiourazoles I shall take up at first the following problems:

(1) The relative velocities of reaction of the two tautomeric forms with other compounds, in different solvents, at different temperatures, etc.

(2) The relative velocities of the rearrangement of each salt into the other, in water and other solvents, at different temperatures, and hence the value of the equilibrium constants; many salts, having various anions and various cations, will be used.

(3) Especially will attention be given to the question whether all these reactions are ionic or molecular or both. It is very important to know whether only the anions of the salts, or the undissociated salts, or more complex ions or double salts, or *all*, rearrange into each other, and whether in the different individual cases the anions, or the undissociated salts (or the cations and anions together), or more complex

salts, or all together, may unite with the alkyl halides and form complex ions, or molecules, which can yield the end products.

All these questions are very complicated and can be solved only by a great amount of accurate work. Conclusions reached must be stated only tentatively and I am presenting my work and ideas only in this light. When the theory is no longer useful as a working hypothesis I shall throw it away.

EXPERIMENTAL.

2,4-Diphenyl-3-thiosemicarbazide.—This compound was made by the method of Busch and Holzmann¹. To 10 grams of phenylhydrazine in 80 grams of alcohol, cooled in a mixture of salt and ice, 12.5 grams of phenyl mustard oil in 25 grams of cold alcohol were added. The semicarbazide separated out and after ten or fifteen minutes was filtered and washed with cold² alcohol. Twenty grams of pure compound melting completely at 139° were obtained.

1,4-Diphenyl-5-thionurazole was made by the method of Busch and Reinhardt.³ One hundred and twenty grams of a 20 per cent. solution of phosgene in toluene, cooled in a mixture of salt and ice, were added to 10 grams of 2,4-diphenyl-3-thiosemicarbazide suspended in 20 cc. of half-frozen benzene. The mixture was shaken thoroughly and allowed to stand in a salt and ice mixture for a few hours, and then at the laboratory temperature. At the end of 48 hours the solid was filtered off, dried on a clay plate and shaken out in a funnel with a liter of very dilute cold caustic potash solution. Then the solid (*a*) remaining was filtered off and the alkaline solution was cooled in ice and acidified with cold dilute hydrochloric acid. The precipitated urazole (*b*) was filtered off immediately; when the filtrate was kept in ice more of the urazole (*c*) separated. The precipitate (*b*) obtained above was dried, shaken out with cold dilute alkali and filtered and the solution acidified. In this way 5 grams of urazole

¹ Ber. d. chem. Ges., **34**, 324. Holzmann: Diss., Erlangen, 1902.

² This substance rearranges into the isomeric 1,4-diphenyl-3-thiosemicarbazide when it is crystallized from hot alcohol, but Mr. E. P. Doetsch has found that it can be nicely purified, without rearrangement, by crystallization from hot benzene.

³ Reinhardt: Diss., p. 66.

were obtained; 2.5^a grams from the second precipitation (b) and 2.5 grams from the filtrate (c). The substance melted completely when dipped into the melting-point bath heated to 141°, and then solidified and melted again at 220°–222°. The substance obtained from the filtrate (c) was perfectly white and dissolved in alkalis, forming a colorless solution, while the urazole which was reprecipitated (b) was slightly brown in color and gave a yellowish solution. The per cent. of thionurazole in each sample can be determined only by an analysis. Some samples contain 90 per cent. thionurazole and others were over 99 per cent. pure.

1-Carbethoxy-2,4-diphenyl-3-thiosemicarbazide,



.—An attempt was made to use this com-

pound for obtaining the 1,4-diphenyl-5-thiolurazole. The method of Busch and Grohmann¹ for making the semicarbazide was tried with no success. The following method gave good yields for a time: Twenty grams of 2,4-diphenyl-3-thiosemicarbazide were dissolved in 150 cc. of neutral chloroform in the presence of 25 grams of finely ground potassium carbonate and the mixture boiled under a return condenser. Then a slight excess of ethyl chlorcarbonate was added, and, after boiling one hour, half of the first amount of ethyl chlorcarbonate was added and the mixture boiled another hour. Then the chloroform solution was shaken out with water to remove the suspended potassium carbonate, dried, and the chloroform distilled off. An oil remained in the flask, which on standing deposited white crystals. Ether was added to the mixture, whereupon more crystals came out. They were filtered off and washed with ether; 7.5 grams of a substance melting at 143°–144° were obtained. The melting point of the compound of Busch and Grohmann was 145°. This substance was obtained several times with equally good yields when suddenly it became impossible to obtain any of it at all. At least 20 experiments were tried under varying conditions

¹ Grohmann: Diss., Erlangen, 1900, p. 20.

and with different solvents but in no case was any of the compound ever obtained again. No apparent reason for this was found. This trouble caused considerable delay in the work, as the compound would have furnished the 1,4-diphenyl-5-thiolurazole easily, in any desired quantity.

1,4-Diphenyl-5-thiolurazole.—This was first made by the saponification of the above ester. It was suspended in a small amount of alcohol and a slight excess of a solution of sodium ethylate added. The crystals soon went into solution, water was added and the solution was acidified; a voluminous precipitate of 1,4-diphenyl-5-thiolurazole was then formed. The substance, when crystallized from alcohol, melted at 221° – 223° . After it was no longer possible to obtain the 1-carbethoxy-2,4-diphenyl-3-thiosemicarbazide, the thiolurazole was made by the rearrangement of the corresponding 1,4-diphenyl-5-thionurazole. For this purpose some of the 1,4-diphenyl-5-thionurazole was put into a test tube and dipped into a paraffin bath at 150° and kept there until it had fused and resolidified. Then it was dissolved in caustic potash and the solution filtered and precipitated with hydrochloric acid. The acid was filtered off and crystallized twice from alcohol. Then it was heated in a test tube to 160° for three hours in order to be certain that it was converted as completely as possible into the 1,4-diphenyl-5-thiolurazole. This was considered necessary, as a mixture of the two acids, containing about 50 per cent. of each, gives no sign of fusion when dipped into the melting point bath at 143° , and a mixture containing 80 per cent. of the 1,4-diphenyl-5-thionurazole barely shows signs of a fusion and resolidification wave traveling through the mixture at 143° . The substance was perfectly white and dissolved in alkalis, giving a colorless solution. It melts at 221° – 223° .¹ *The constancy of the melting point gives no clue regarding the relative percentages of the thiol- and the thionurazoles, and these experiments should be borne in mind in all work on tautomeric compounds. The ratio can be determined only by an analysis, as discussed later, and when I speak of the thiol- and thionurazoles I do not*

¹ Reinhardt: Diss., 1906.

mean that they are necessarily free from each other, unless it is definitely so stated.

Alkylation of 1,4-Diphenyl-5-thionurazole and 1,4-Diphenyl-5-thiolurazole with Diazomethane and -ethane.—In the earlier part of the work it was intended to study the rearrangement of the two acids by adding a diazoalkyl, and analyzing the mixture of esters obtained. On studying the action of diazomethane and -ethane on the two urazole acids, however, it was found that the esters obtained are different from those made from the sodium salts and methyl iodide. None of them split out methyl sulphhydrate when heated with caustic potash, but they are decomposed, and give off hydrogen sulphide when the mixture is acidified.

Two grams of 1,4-diphenyl-5-thionurazole were suspended in ether and an ethereal solution of diazomethane was added until the yellow color of the diazomethane persisted. Then the ether was evaporated off. An oil remained which solidified on standing a week in a vacuum desiccator. The solid, after being washed twice with cold alcohol, melted at $74^{\circ}.5-75^{\circ}.5$. Analysis showed that it had the composition $C_{15}H_{13}ON_3S$. Yield, 1.2 grams. From 0.1210 gram of the ester heated 5 minutes at 90° , with a 3 per cent. solution of alcoholic potash, 0.015 gram of unchanged substance was obtained. Several other similar experiments were tried under different conditions of temperature, but with results of the same nature. One gram of 1,4-diphenyl-5-thionurazole under the same conditions gave, with diazoethane, an oil from which, on solidification and crystallization from alcohol, an ester melting at $79^{\circ}-81^{\circ}$ was obtained. Yield, 0.5 gram. The analysis showed it to have the composition $C_{16}H_{15}ON_3S$.

Two grams of 1,4-diphenyl-5-thiolurazole, when treated with diazomethane, gave an ester which, when crystallized twice from alcohol, melted at $129^{\circ}.5-130^{\circ}.5$ (uncor.). Analysis showed it to be isomeric with the ester obtained from 1,4-diphenyl-5-thionurazole and diazomethane: 0.1847 gram of this ester when heated one hour at 100° with 5 cc. of a 10 per cent. alcoholic solution of potassium hydroxide, gave back 0.0215 gram of unchanged ester. In another case, 0.0315

gram unchanged substance was obtained from 0.0864 gram ester on heating it 15 minutes at 100° with 5 cc. of 3 per cent. caustic potash. Results of a like character were obtained in experiments at 50° . 1,4-Diphenyl-5-thiolurazole and diazoethane gave an ester which, when crystallized from ligroin, melted at $105^{\circ}.5-107^{\circ}.5$. The fact that diazomethane does not give the 5-thiolurazole methyl ester melting at 196° is strong proof, with other such cases, that the diazoalkyls cannot be *absolutely* depended upon to give derivatives corresponding to the mother substance.

Owing to the fact that neither of the compounds obtained by treating the two acids with diazomethane reacted in a definite way with caustic potash it was impossible to separate the two, and consequently this phase of the work had to be abandoned. I shall later take up these reactions exhaustively. On account of the fact that diazomethane forms ring compounds with unsaturated substances, which double compounds may decompose further in some cases, it may be difficult to trace the relation between the constitution of the ester and that of the acid from which the ester is obtained.

Preliminary Experiments on the Alkylation of Sodium 1,4-Diphenyl-5-thionurazole and Sodium 1,4-Diphenyl-5-thiolurazole.—No attempt was made to isolate the sodium salts of the two acids, but in all cases the weighed amount of acid was titrated with the corresponding amount of sodium hydroxide. That this procedure can be used is shown by the following figures:

0.3983 gram of 1,4-diphenyl-5-thionurazole required 29.50 cc. 0.05 N NaOH. The calculated amount is 29.60 cc.

0.4050 gram of 1,4-diphenyl-5-thiolurazole required 30.20 cc. 0.05 N NaOH. The calculated amount is 30.08 cc.

Owing to the fact that Reinhardt¹ was unable to obtain the esters of the two acids from the sodium salts and methyl iodide the conditions governing the preliminary experiments were carefully watched. It was soon found, however, that at 50° or 60° or even at lower temperatures, large yields of

¹ *Loc. cit.*

the esters of the two acids can easily be obtained in a short time. It was simply necessary to add an alcoholic solution of methyl iodide to an aqueous solution of the sodium salt, and to heat this at 50° or 60° for an hour or two. Later when 20 molecules of methyl iodide (always in alcohol) were used, nearly quantitative yields of ester were obtained from each of the acids in 20 minutes.

The velocity of alkylation of the two salts with methyl iodide was first studied in order to obtain their relative reactivities. The procedure was as follows:¹

1,4-Diphenyl-5-thionurazole (0.4039 gram) was weighed in a tube sealed off at one end and 3 cc. 0.5 N NaOH were run in from a burette. After the acid had dissolved, 2 cc. of 0.75 N solution of methyl iodide in ethyl alcohol were added, the tube sealed off, and put in the constant temperature bath and shaken. At the end of the time period t , it was taken out, cooled in ice water and opened, and the contents poured into an extraction funnel containing very dilute alkali. The ester² was extracted by shaking out the solution 6 times with chloroform. The chloroform was evaporated off below its boiling point in a weighed porcelain dish and the ester dried to constant weight, x , in a vacuum desiccator. The results of these quantitative experiments are given in Table I below.

That the extraction removes nearly all of the ester from the solution is shown by the following figures:

After 0.2955 gram methyl 1,4-diphenyl-5-thionurazole ester was extracted 6 times with dilute caustic potash, 0.2922 gram, or 98.87 per cent., was removed.

From 0.2949 gram methyl 1,4-diphenyl-5-thiolurazole, treated as above, 0.2920 gram ester, or 99 per cent., was recovered.

¹ Ber. d. chem. Ges., **41**, 3199.

² I have shown that this ester is a mixture of two thion esters—a N-ester [(V), page 44], and an O-ester [(VI), page 44]. I have not determined the ratios of these two esters, but this problem has been studied by Mr. E. P. Doetsch. The fact that this thion salt may be an equilibrium mixture of the $=N-Na$ and $-N=C(ONa)$ salt does not change the relations presented in this article.

Table I.—0.3 Wt. N Sodium Salt of 1,4-Diphenyl-5-thionurazole and 0.3 Vol. N Methyl Iodide in Ethyl Alcohol at 50°.

<i>t</i> (minutes).	<i>A</i> .	<i>x</i> .	<i>A</i> — <i>x</i> .	<i>AK</i> .
30	0.4249	0.1103	0.3146	0.0117
60	0.4249	0.1705	0.2544	0.0112
180	0.4249	0.2882	0.1367	0.0117
240	0.4249	0.3071	0.1178	0.0109
Average,				0.0114

The ester obtained was a viscous reddish oil, which, on standing, became semisolid.

The sodium 1,4-diphenyl-5-thiolurazole is so reactive with methyl iodide that no constants could be obtained at 50°. For example, 3 cc. 0.5 N sodium 1,4-diphenyl-5-thiolurazole and 2 cc. 0.75 vol. normal methyl iodide, at 50°, gave, in two hours, 0.3511 gram ester. In 5 minutes, at 25°, over 0.3 gram ester was obtained. In 15 minutes, at 60°, under the same conditions, 0.3584 gram ester was obtained, while in 4 hours only 0.3358 gram was found. This shows that practically all the ester is formed in a few minutes, and that it then slowly decomposes. This is also shown by the fact that on opening the tubes there was a strong odor of methyl mercaptan. The ester obtained was perfectly white and after one crystallization from alcohol and drying on the water bath melted sharply at 196°–197° to a clear, colorless liquid. It was identical with the ester obtained by treating 2,4-diphenyl-3-methylthiosemicarbazide with phosgene; a mixture of the two samples melted at 196°.

Since the thiol salt reacts so rapidly with methyl iodide at 25° or 50°, it was evident that the study of the reaction velocity must be done at 0°. The following table shows the data obtained in 50 per cent. alcohol by Mr. E. P. Doetsch.

If we assume a temperature coefficient of 2 for an increase of 10° *AK* would be 0.1344 at 50°. This means, when differences in concentration are considered, that the sodium thiol salt reacts about 80 times as rapidly with methyl iodide as does the sodium salt of 1,4-diphenyl-5-thionurazole.

Table II.—0.045 N Sodium Salt of 1,4-Diphenyl-5-thiolurazole and 0.045 N Methyl Iodide at 0°.

<i>t</i> (minutes).	A.	<i>x</i> .	<i>A</i> — <i>x</i> .	AK.
30	0.2394	0.0327	0.2067	0.00527
30	0.2394	0.0298	0.2096	0.00473
60	0.2394	0.0457	0.1937	0.00393
120	0.2394	0.0712	0.1682	0.00353
240	0.2394	0.1160	0.1234	0.00391
360	0.2394	0.1396	0.0998	0.00388
990	0.2394	0.2018	0.0376	[0.00540]
1265	0.2394	0.2097	0.0297	[0.00552]

Average AK = 0.0042

When the tubes were opened only a faint odor of mercaptan was observable, a proof that the thiol ester is hardly hydrolyzed at 0°.

Hydrolysis and Separation of the Esters.—Owing to the easy decomposition of the 1,4-diphenyl-5-methylthiolurazole by caustic potash into methyl mercaptan and potassium 1,4-diphenylurazole, it was at the beginning recognized that this would be the easiest way to separate this ester from a mixture containing it and the methyl esters of 1,4-diphenyl-5-thionurazole.

It was not so easy, however, to find an experimental method to hydrolyze this ester quantitatively, and at the same time not appreciably decompose the esters of the 1,4-diphenyl-5-thionurazole. In the preliminary experiments with 1,4-diphenyl-5-thiolurazole, a weighed amount of ester and enough alcohol to dissolve the ester was put in a porcelain dish on the water bath, and then various amounts of alkali were added. This method is easier than that involving the sealed tubes which I have used several years, although not so accurate. After a certain time the contents of the dish were washed into a funnel and the unhydrolyzed substance extracted with chloroform. Then the solution was acidified and the precipitated 1,4-diphenylurazole was extracted with chloroform and weighed as a check. The following results were obtained:

Weight of ester.	Amount of alkali.	Time heated (minutes).	Amount not hydrolyzed.	Per cent.	Per cent. of 1,4-diphenyl urazole recovered.
0.1995	10 cc. 0.25 N	20	0.0007	0.35	93.0
0.2047	10 cc. 0.50 N	20			92.2
0.1546	20 cc. 0.50 N	15	0.0004	0.25	96.0

This shows conclusively that the 1,4-diphenyl-5-methylthiolurazole can be hydrolyzed practically quantitatively. But when the oily esters of 1,4-diphenyl-5-thionurazole were treated by the above method they were not only badly decomposed, but the oil floated on top of the alkali and crept over the side of the dish. On this account the experiments in open dishes were abandoned. Then the methyl thiol ester was heated at 60° in sealed tubes with various amounts of alkali the tubes being shaken during the hydrolysis.

Weight of ester.	Amount of alkali.	Time of hydrolysis.	Amount not hydrolyzed (grams).	Per cent.
0.1460	10 cc. 0.25 N KOH	16 hrs.	0.0004	0.28
0.1017	10 cc. 0.10 N KOH	35 min.	0.0015	1.4

In the actual experiments, however, it is necessary to use chloroform in transferring the esters from the dishes in which they were weighed. The greater part of the chloroform is evaporated off, but one or two cc. always remain with the ester, and this is generally eliminated by repeated evaporation with small quantities of pure ether. I then introduced the "Künstgriff" of testing whether the methyl thiol ester could be hydrolyzed in the presence of chloroform in the tubes at 60°.

In the following experiment a weighed amount of 1,4-diphenyl-5-methylthiolurazole was put into tubes sealed off at one end and then 2 cc. chloroform and a certain amount of alkali were added. The tubes were sealed off at the other end and heated at 60°:

Weight of ester.	Amount of alkali.	Time of hydrolysis.	Amount not hydrolyzed (grams).	Per cent.
0.0835	10 cc. 0.1 N KOH	1 hour	0.0006	0.72

Then the methyl thion esters were treated in the same way.

These esters were obtained by alkylating sodium 1,4-diphenyl-5-thionurazole and extracting the ester with chloroform as explained before. After the ester had come to constant weight in the dish it was transferred to the small tubes drawn out to a capillary at one end, and the chloroform evaporated down to 1 or 2 cc. Then the tube was constricted at the other end, the alkali added and the tube sealed off. The tubes were heated at 60° with constant shaking:

	Weight of ester.	Amount of alkali.	Time of hydrolysis (hours).	Amount not hydrolyzed (grams).	Per cent. not hydrolyzed.
1	0.2477	10 cc. 0.1 N KOH	1	0.2385	96.2
2	0.2950	10 cc. 0.1 N KOH	1	0.2883	97.7
3	0.1724	10 cc. 0.1 N KOH	1	0.1684	97.6
4	0.1684	10 cc. 0.1 N KOH	1	0.1674	99.4

In experiments 1, 2 and 3 the ester was taken in the condition in which it was obtained from the action of methyl iodide and sodium 1,4-diphenyl-5-thionurazole. We should expect some loss here due to the formation of the methyl thiol ester from that part of the salt which rearranged into the other form during the alkylation, and from some of the thiol salt present originally. Experiment 4 is of especial importance, as in this case the ester remaining after hydrolysis in experiment 3 was used. This is the real test of my method and we see that in the presence of the chloroform the methyl esters of 1,4-diphenyl-5-thionurazole are not appreciably attacked by dilute caustic potash at 60°.

Then experiments were tried with mixtures of the methyl esters. The procedure was that used above, the methyl thiol ester being weighed into the tubes before the other ester had been washed in by means of chloroform:

Thiol ester.	Thion ester.	Alkali.	Weight of unhydrolyzed ester.	Time.
0.0623	0.2278	8 cc. 0.25 N KOH	0.2291	2
0.0510	0.2258	8 cc. 0.25 N KOH	0.2255	2

By this procedure, then, the esters are separated quantitatively, the methyl thiol ester being hydrolyzed and giving methyl sulphydrate and 1,4-diphenylurazole, while the oily methyl esters of 1,4-diphenyl-5-thionurazole remain in the

chloroform and are not greatly affected by the alkali. The 1,4-diphenylurazole can be recovered to the extent of about 95 per cent. by acidifying the aqueous solution in the funnel, and extracting with chloroform.

It was at once realized that if the esters were to be used as a means of analyzing the mixture of salts at any moment a method must be devised for alkylating the salts quantitatively in a short time and giving a ratio of esters corresponding to the ratios of the two salts. Since other researches in the urazole group have shown that the ratio of esters may change with the change in solvent I decided to try first a mixture of water and alcohol. Mr. E. P. Doetsch has since learned that the presence of the alcohol has a serious disturbing effect on the apparent ratios of the salts, and that the hydrolysis of the thiol ester during the alkylation must be suppressed by making the solution *neutral* by adding a mixture of mono- and disodium phosphates or other similar compounds. The results of the present investigation must therefore be considered as preliminary.

After various experiments it was found that 20 molecular equivalents of methyl iodide and either salt, in about 7 cc. of 60 per cent. alcohol, will give practically quantitative yields of ester, at 60°, in from 15 to 20 minutes. From 0.404 gram 1,4-diphenyl-5-thionurazole, 0.417 gram methyl ester was obtained. The theoretical amount is 0.425 gram. Furthermore, 0.404 gram of 1,4-diphenyl-5-thiolurazole gave 0.409 gram ester under the same conditions. Then the two salts (0.2 gram) were alkylated and the esters analyzed in order to determine the purity of the acids used:

1,4-Diphenyl-5-thionurazole.

	Weight of ester.	Weight of ester after hydrolysis.	Loss.	Per cent purity of acid.
1	0.2022	0.1934	0.0088	95.65
2	0.1976	0.1914	0.0062	96.86

1,4-Diphenyl-5-thiolurazole.

1	0.1690	0.0198	0.1492	88.29
2	0.1843	0.0215	0.1628	88.34
3	0.1818	0.0195	0.1623	89.3
4	0.1843	0.0187	0.1656	89.86

It is seen in this last table that the alkylations were not complete. As a final check on the method, known weights of the two acids were mixed, the theoretical amount of sodium hydroxide added and the salts alkylated. Then the esters were analyzed. In calculating the actual amount of each acid in the mixture the 1,4-diphenyl-5-thionurazole was taken as being 96.25 per cent. pure, and the 1,4-diphenyl-5-thiolurazole as being 89 per cent. pure:

Weight of 1,4-diphenyl-5-thionurazole (1) (gram).	Weight of 1,4-diphenyl-5-thiolurazole (2) (gram).	Calculated per cent. of (1) in total acid.	Found.
0.1020	0.100	53.9	55.6
0.0455	0.1565	30.5	31.7
0.1465	0.0555	72.6	71.5
0.1000	0.1020	52.9	53.5
0.1500	0.0520	74.2	73.6

The check experiments described in this section show that the method, taken as a whole, is accurate to well within 5 per cent. A more systematic study of the time and the concentration of alkali necessary for complete hydrolysis of the methyl thiol ester, and the conditions for complete alkylation of the salts, would without doubt reduce the maximum error to 2 or 3 per cent. The results of the rearrangement experiments described below appear, on the surface, to be very satisfactory. Such, however, is not the case and this fact must serve as a warning against the hasty acceptance of mere mathematical concordance of the results. In this physical-organic research there are so many uncertainties until each problem is studied deeply that the conclusions can be only tentative.

Rearrangement Experiments.—While the method of analysis of the salt mixtures was being worked out, preliminary experiments were made on the rearrangement of sodium 1,4-diphenyl-5-thionurazole. The first experiments were carried out at 100°. Three cc. of a 0.5 weight N solution of sodium 1,4-diphenyl-5-thionurazole were sealed in a small tube holding about 6 cc. and the tube was fastened in the neck of a flask half full of rapidly boiling water. After certain intervals the tubes were opened and 2 cc. of 0.75 vol. N methyl iodide

in ethyl alcohol¹ were run in and the tubes were sealed up again. This made the whole solution approximately 0.3 N. After heating two hours at 60° the contents of the tubes were poured into extraction funnels and the esters were extracted with chloroform and weighed. In one experiment lasting twenty-two hours, practically pure methyl ester of 1,4-diphenyl-5-thiolurazole was obtained on alkylation, so no further work was done at 100°. Then tubes were heated in the same way at 60° and alkylated. After heating one tube eleven hours and then alkylating, 0.201 gram of ester was obtained which contained 80 per cent. of the esters of 1,4-diphenyl-5-thionurazole. Although only about half of the salt had been alkylated, this indicated very well that the reaction could be studied at 60°.

Meanwhile the method for the analysis of the mixture of salts had been worked out, so the procedure finally adopted was as follows: 0.202 gram of 1,4-diphenyl-5-thionurazole was weighed into a tube holding about 8 or 9 cc. and the tube was drawn out to a long capillary at the open end. Then 1.5 cc. of 0.5 N sodium hydroxide and 1.5 cc. of water were run in and the tubes sealed off. This made the solution 0.25 weight N with respect to the salt. The tubes were put into a bath² kept at 60° for certain time periods and then taken out. The very tip of the capillary was broken off and 4 cc. of 3.75 vol. N methyl iodide were run in, the capillary was sealed up again and the tube then put back into the bath. At the end of twenty minutes it was taken out, opened, and the contents were poured into a separating funnel containing water to which a few drops of alkali had been added. The ester was extracted with 6 portions (5 cc. each) of chloroform, the chloroform was evaporated off in a weighed porcelain dish, and the ester was then dried to constant weight at 55° in an air bath. The ester was transferred by means of chloroform to small tubes, drawn off to a capillary at the lower end, and

¹ As stated above, the alcohol should not be used. Mr. E. P. Doetsch has shown that when the alcohol is present there is a more rapid change of the ratio of the salts during the alkylation than when water alone is used. While my results are fairly concordant, they are only tentative.

² For a description of the bath used see Brunel and Acree: *Am. Chem. Jour.*, **43**, 533.

the solvent was evaporated down to about 2 cc. by dipping the capillary part of the tube into a water bath at 80°. *To prevent bumping a capillary stirring rod is inserted well down into the capillary end of the tube.* Then 5 or 6 cc. of half-normal potassium hydroxide were added and the tubes sealed off. They were shaken for two hours in the 60° bath, and opened, and the unhydrolyzed ester extracted in the usual way. The following table shows the results obtained in a large number of experiments:

Table III.

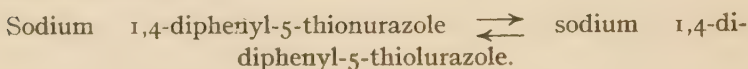
Time (hours).	Weight of total ester.	Weight of unhydrolyzed ester.	Per cent. thion ester (C—C ₂).
0	0.1976	0.1914	96.8
	0.2022	0.1934	95.7
6	0.1987	0.1775	89.3
	0.2010	0.1800	89.5
12	0.2058	0.1652	80.3
	0.2037	0.1625	79.8
18	0.2110	0.1565	74.2
24	0.2007	0.1410	70.4
36	0.1977	0.1374	69.7
	0.1705	0.1083	63.5
	0.1945	0.1230	63.2
42	0.2013	0.1192	59.2
96	0.1726	0.0556	32.3
	0.1618	0.0516	31.9
168	0.1584	0.0384	24.2
216	0.1732	0.0343	19.8
	0.1686	0.0319	18.9
336	0.2019	0.0204	10.1

Experiments were carried out in the same way with sodium 1,4-diphenyl-5-thiolurazole.

Table IV.

Time (hours).	Weight of total ester.	Weight of unhydrolyzed ester.	Per cent. thion ester (C—C ₂).
0	0.1690	0.0198	11.7
0	0.1843	0.0215	11.7
0	0.1818	0.0195	10.7
0	0.1843	0.0187	10.1
48	0.1868	0.0214	11.5
120	0.1760	0.0280	15.9
	0.1805	0.0295	16.3

These figures show that the reaction is slightly reversible and that we have:



If the reaction is monomolecular¹ then

$$(1) \frac{dc_2}{dt} = K_1(C - C_2) - K_2(C_1 + C_2),$$

where C is the original concentration of the sodium 1,4-diphenyl-5-thionurazole, C_1 that of the sodium 1,4-diphenyl-5-thiolurazole present at first, and C_2 that of the rearranged salt.

At equilibrium,

$$\frac{K_1}{K_2} = \frac{C_1 + C_2}{C - C_2},$$

Substituting $\frac{K_1}{K_2} = K$ in equation (1) and integrating we get

$$\frac{1}{t} \log \frac{KC - C_1}{KC - C_1 - (K + 1)C_2} = K_1 + K_2.$$

Since in a unimolecular reaction the unit of concentration is immaterial we can assume that C is 96.25 and C_1 is 3.75. The experiments given above do not give the definite equilibrium ratio but the most probable one is the value for sodium 1,4-diphenyl-5-thionurazole heated for 336 hours, where C_2 is equal to 96.25-10.1, or 86.15. Then,

$$K = \frac{K_1}{K_2} = \frac{3.75 + 86.15}{96.25 - 86.15} = 8.9$$

Table V.

t .	C .	C_1 .	C_2 .	$K_1 + K_2$.	K_1 .	K_2 .
6	96.25	3.75	6.9	0.0061	0.0055	0.00061
12	96.25	3.75	16.3	(0.0076)	(0.0068)	(0.00076)
18	96.25	3.75	22.1	0.0071	0.0064	0.00071
24	96.25	3.75	26.3	0.0066	0.0059	0.00066
36	96.25	3.75	33.0	0.0058	0.0052	0.00058
42	96.25	3.75	37.1	0.0060	0.0054	0.00060
96	96.25	3.75	64.2	0.0062	0.0056	0.00062
168	96.25	3.75	72.3	(0.0047)	(0.0042)	(0.00047)
216	96.25	3.75	76.9	(0.0045)	(0.0041)	(0.00044)

¹ In the equations no account is taken of the question whether the molecules or the ions of the salts undergo transformation. In either case it would merely be necessary to substitute for c and c_1 the values αc or $(1-\alpha)c$, and $\alpha'c_1$ or $(1-\alpha')c_1$ and hence introduce new constants. According to the isohydric principle α and α' should be practically constant during the reaction. It is also not greatly material whether c or c_1 represents a mixture of two salts in nearly instantaneous equilibrium.

This series, while only preliminary, shows apparently that the reaction is monomolecular and especially that the salts rearrange into each other. It is especially to be regretted that in many of the experiments in the above tables the weight of ester is much below the theoretical. As stated above, however, Mr. E. P. Doetsch has obtained better results where no alcohol is present.

Conclusions.

1. It has been shown that the compound supposed by others to be 1,4-diphenyl-5-thiolurazole is in reality 1,4-diphenyl-5-thionurazole, and that the one supposed by them to be 1,4-diphenyl-5-thionurazole is 1,4-diphenyl-5-thiolurazole.

2. This work shows that we can convert these two acids into salts which have two different tautomeric forms, one corresponding to the structure of 1,4-diphenyl-5-thionurazole and the other corresponding to the structure of 1,4-diphenyl-5-thiolurazole. These two salts not only give back their corresponding acids on the addition of hydrochloric acid, but they also give their own characteristic derivatives. The silver salts of the two acids are also different. The two sodium salts have each been alkylated with equivalent amounts of methyl iodide. The sodium 1,4-diphenyl-5-thionurazole and methyl iodide in 0.3 N solution (40 per cent. alcohol) at 50° give a very good constant, $AK = 0.0114$, only about 75 per cent. of the salt being alkylated in 4 hours at 50°. The sodium 1,4-diphenyl-5-thiolurazole is alkylated 75 per cent. in 5 minutes at 25°, while this salt and methyl iodide in 0.045 N solution (50 per cent. alcohol) at 0° give the constant $AK = 0.0042$. If we assume a temperature coefficient of 2 for each 10° and take into consideration differences in concentration, the experiments show that methyl iodide reacts about 80 times as rapidly with the sodium salt of 1,4-diphenyl-5-thiolurazole as it does with the other sodium salt, and this fact gives further evidence that we have assigned the correct structure to the higher-melting form.

3. The sodium salts of these two acids have been esterified

quantitatively and a method, accurate to within 5 per cent., has been devised for analyzing a mixture to the two salts. A mixture of the esters can be analyzed accurately with an error of 2 or 3 per cent.

4. It is shown further that the sodium salts are mutually convertible into each other through two apparently reversible unimolecular reactions, and that the velocity of rearrangement of the sodium 1,4-diphenyl-5-thionurazole is approximately 9 times as large as that of sodium 1,4-diphenyl-5-thiolurazole. The thiol salt is less reactive in this reversible change but much more reactive in the alkylation experiments. A study of the relationship of the energy changes involved in the two reactions is of the greatest importance.

5. Work with these compounds should throw great light on tautomerism. We can actually isolate the tautomeric acids and their corresponding salts, and can study accurately many of the tautomeric phenomena exhibited by these substances. Other types of tautomeric compounds, such as acetacetic ester, cyanides, cyanates, nitrophenols, phenolphthaleins, oximes, amidines, and many others, whose properties do not so readily admit of such quantitative study, exhibit many of the tautomeric phenomena belonging to the urazoles. It is therefore possible that further work on these urazoles will help us to understand more about the large number of classes of substances known under the name of tautomeric compounds.

BIOGRAPHY.

Sidney Nirdlinger, the author of this dissertation, was born in Galesburg, Illinois, April 4, 1887. His early education was obtained in the public schools of Galesburg and in 1902 he graduated from the High School. He then entered Knox College, at Galesburg, and graduated in 1906 with the degree of B.S. In the fall of 1906 he entered Johns Hopkins University as a graduate student in Chemistry, with Physical Chemistry and Physics as his subordinate subjects. During the years 1907-8 and 1908-9 he held graduate scholarships.



